STUDIES ON THE CHEMICAL SIMULATION OF THE ATP-IMIDAZOLE CYCLE

A Thesis Submitted
In Partial Fulfilment of the Requirements
for the Degree of
DOCTOR OF PHILOSOPHY

by

KRISHNAN KESAVAN

to the
DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY KANPUR
JUNE, 1983

Science in the making, science as an end to be pursued, is as subjective and psychologically conditioned as any other branch of human endeavour.

Albert Einstein

If I had to write a book on morality, it would have a hundred pages and ninetynine would be blank. On the last page I should write. "I recognise only one duty, and that is to love". And as far as anything else is concerned, I say "No".

Albert Camus

DEDICATED

TO

MY PARENTS

STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology, Kanpur, India, under the supervision of Professor S. Ranganatha

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigat

K. KESAVAN

CERTIFICATE

Certified that the work contained in this thesis, entitled, "STUDIES ON THE CHEMICAL SIMULATION OF THE ATP-IMIDAZOLE CYCLE" has been carried out by Mr. Krishnan Kesavan under my supervision and the same has not been submitted elsewhere for a degree.

Kanpur
June, 1983

S. Ranganathan
Thesis Supervisor

DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY, KANPUR, INDIA

CERTIFICATE OF COURSE WORK

This is to certify that Mr. K. Kesavan has satisfactorily completed all the course requirements for the Ph.D. degree programme. The courses include:

Chm	501	Advanced Organic Chemistry I
Chm	502	Advanced Organic Chemistry II
Chm	521	Chemical Binding
Chm	524	Modern Physical Methods in Chemistry
Chm	581	Basic Bio-Chemistry and Molecular Biology
Chm	801	Graduate Seminar
Chm	900	Graduate Research
Chm	800	General Seminar

Mr. Krishnan Kesavan successfully completed his Ph.D. qualifying examinations in January, 1980.

(U.C. Agarwala)
Professor and Head
Department of Chemistry

(S. Chandrasekaran)
Convenor
Department Post-Graduate Committee

ACKNOWLEDGEMENTS

I want to express my gratitude to Professor S. Ranganatha for initiating me into the realm of research in organic chemistr assigning the problem and for his constant guidance and support, till its production in its final form.

I am, indeed, indebted to Dr.(Mrs.) D. Ranganathan for her association in this work, heart and soul, sisterly affectio bestowed and encouragement given in time of need.

Presence of Master Anand Kumar Ranganathan lent a homely atmosphere.

Indeed, I owe a great deal to Professors S. Ranganathan, M.V. George, P.T. Narasimhan, P. Raghunathan, S. Chandrasekaran and S.K. Dogra for teaching the theoretical aspects of various branches of chemistry at the most advanced levels.

My sincere thanks are due to my colleagues in the lab, Ramachandran, Shakti, Sanjiv, S.K. Singh, W.P. Singh, G.P. Singh and F. Farooqui for their pleasant association. Special mention must be made of Sanjiv, Manisha and Jayanthi Chandrasekaran who were associated with the progress of this work at various stages.

I want to express my thanks to Dr. M.M. Mehrotra, Harvard University, U.S.A., Dr. A.K. Mehrotra, Milwaukee, U.S.A., and Dr. K. Raman, Delaware, U.S.A. for many of the nmr spectra reported in the thesis.

Thanks are also due to Dr. Nityanand, Dr. S.P. Popli, Dr. R.S. Kapil of CDRI, Lucknow, Dr. S. Rajappa of CIBA-GEIGY, Bombay and Dr. Ravindranathan, NCL, Poona for many of the nmr and mass spectra.

Thanks are due to Rajagopalan and Nayab for ir and elemental analysis. The services of Central Glass-Blowing facility is gratefully acknowledged.

Amongst friends, who made extra-laboratory hours cheerful special mention must be made of Ramachandiran, Raghunathan, Balakrishnan, Sriraman, Rao, Govindarajan, Swaminathan, Arulswamy Shankar, Keshav and Reddy.

I am thankful to Professor and Mrs. Ranganathan, Professor M.V. George, Professor P.T. Narasimhan, Chandrasekarans, Sathyamurthys and Raghunathans for their encouragement and concern in my growth.

My special thanks to Mr. Anil Kumar for excellent typing and to my friends who helped me in production of the thesis.

To my parents, who could spare me, for my good, in their hour of need, to my wife, brother, sisters and in-laws who evinced great care in my growth.

Finally, I am grateful to the 'University Grants Commission for financial assistance, the Government of Tamil Nadu

and the Director of Collegiate Education for their kind consent to pursue the research programme and the authorities of IIT, Kanpur for providing research facility.

K. KESAVAN

STUDIES ON THE CHEMICAL SIMULATION OF THE ATP-IMIDAZOLE CYCLE

An attractive facet of the art in organic synthesis would be the creation of structures on a template which can be re-cycled. Such a strategy has been - although used by Nature for the bio-synthesis of structures vitally associated with life processes - neither exploited nor systematically explored thus far. A unique example of template strategy in Nature is the "ATP-Imidazole" Cycle wherein a daughter imidazole is grown on a mobile parent imidazole *via* a cyclic pathway that is linked to the bio-synthesis of the purine codes ATP and GTP as well as to the imidazole amino acid histidine. The cycle is initiated by 5-aminoimidazole-4-carboxamide by acceptance of elements of formic acid to give hypoxanthine which is aminated to adenine and then to, by specific 1-alkylation with acetaldehyde equivalent, followed by Schiff base formation, hydrolysis cyclisation and cleavage to the daughter 5-substituted imidazole and the parent imidazole, which now can initiate another cycle.

The strategy of "growing" the daughter on the parent, 5-aminoimidazole-4-carboxamide, can be analysed in terms of the step-wise introduction of the needed 1-nitrogen and 3-carbons with the amide nitrogen of the parent destined to be part of the daughter imidazole. The protocol involves 3-stages, namely

1. the introduction of the carbon bridge that connects the 2-nitrogen functionalities of the parent.

2. the specific N^1-alkylation of the hypoxanthine system thus formed with $-CH_2-\overset{d}{C}=N-b$.

3. the cyclisation of the ligand thus introduced followe by the separation of the parent from the daughter by hydrolytic processes.

In principle, Nature's versatility can be further augmented, leading to template synthesis of a host of heterocyclic compounds, by affixing the operating part of the ATP-Imidazole Cycle, namely, the vicinally disposed aminocarboxamid unit to an aromatic ring, whence the template is re-designated as anthranilic acid amide. Incorporation of the 1-carbon bridg to this, will now give 3,4-dihydro-4-oxoquinazoline in place of hypoxanthine of the 'ATP-Imidazole' Cycle. Since, 3,4-dihydro-4-oxoquinazoline can be directly obtained from anthranilic acid with formamide, anthranilic acid would be the more appropriate model template. This modification may offer several advantages compared to the fragile, multifunctional imidazole moiety that supports the operating part of the ATP-Imidazole Cycle. Furthe the 3-atom ligand to be introduced in the specific-N-alkylation can be varied, leading to the synthesis of a variety of heterocyclic systems, regenerating the parent.

The present work, with focus to chemically simulate the salient features of the 'ATP-Imidazole' Cycle, incorporates two stages of endeavours. The first is related to the preparation of specifically and appropriately N-substituted ligands from either 3,4-dihydro-4-oxoquinazoline related to the model template anthranilic acid or from hypoxanthine or adenine related to the template 5-aminoimidazole-4-carboxamide.

The second stage envisages the transformation of the specifically alkylated products, obtained from the first stage, to the template and product molecules. It was anticipated that these objectives, pertaining to the second stage, can be attained by three distinctly different pathways, namely,

1. cleavage of the $-\overset{O}{\overset{\|}{C}}-N-$ as in ATP-Imidazole Cycle, or

2. cyclisation to a tricyclic system, or

3. regiospecific hydrolytic cleavage leading to the specific attachment of the resulting CHO function to the amide nitrogen of the template parent. Each of these pathways can lead to the product molecule and the parent either by convergent or divergent pathways.

It was proposed to prepare the required substrates, pertaining to the first stage, by specific N-attachment to the templates in order that they may be transformed to the product molecules. The N^3-alkylated systems thus prepared from model

template anthranilic acid could be anticipated to lead to, *via* pathways similar to that of the ATP-Imidazole Cycle, diverse heterocycles. Thus, the 3-allyl can lead to pyrrole, the 3-(2'-oxoethyl) to oxazole, the 3-(2'-oximinoethyl) to N-hydroxy imidazole, the 3-(2'-iminoethyl) to imidazole, the 3-(2'-hydroxyethyl) to oxazoline, the 3-(2'-aminoethyl) to imidazoline and the 3-aminobenzoyl to oxadiazoline.

The reaction of anthranilic acid (1)* with formamide gave 3,4-dihydro-4-oxoquinazoline (2) in excellent yields which was transformed readily to the 6-nitro analog 3.

Reaction of 2 with $POCl_3$ gave 4-chloroquinazoline (4) which on treatment with CH_2=CH-CH_2-ONa gave the O-allylether 5. Compound 5 underwent smooth [3,3] shift with O → N migration leading to the specifically N-alkylated product 6. Compound 6 on treatment with OsO_4-periodate gave aldehyde 7, which surprisingly was found to exist under normal conditions as a "hydrate" to which the novel tricyclic structure 9 has been assigned. Either aldehyde 7 or the 'hydrate' 9 gave the expected oxime 10 in good yields. Having a set of authentic N-alkylated compounds at hand, endeavours were made to define conditions under which they may be prepared directly. In the event, the reaction of the sodium salt of 2 in HMPA with $BrCH_2CH(OEt)_2$ gave the desired

---

* These numbers refer to those presented in the thesis, Section C.

alkylated product 8. Other alkylation conditions were not successful. Compound 8 was correlated to 9, by treatment with warm conc. H_2SO_4 and to 10 with hydroxylamine hydrochloride.

Reaction of 9 with NH_3 in refluxing benzene gave, instead of the expected Schiff base, the "ammonia adduct" for which the tricyclic structure 11, analogous to that for 9, has been proposed. The propensity of either 7 or the Schiff base, which is believed to have been generated in the reaction, to exist in the tricyclic form, a behaviour that was further encountered in the present work (vide infra), can be attributed to the great tendency exhibited by the 1-2 bond for addition. This tendency was again visible on treatment of 8 with formamide which gave the 'formamide adduct' of the N-formyl Schiff base, for which structure 12 has been assigned.

Parenthetically, compounds 9, 11, 12 and others encountered in the present work, although could be processed through the cycle, could not be further transformed to useful intermediates, because of their tendency to exist in equilibrium with the open structures. Reaction of 9 with aniline gave instead of the expected Schiff base, the dimer 13.

A parellel set of compounds were readily prepared from 6-nitro-3,4-dihydro-4-oxoquinazoline (3). The reaction of the conjugate base of 3 with allylbromide gave the N-allyl derivative

14. Alkylation of 3 with $BrCH_2CH(OEt)_2$ in HMPA gave the expected ketal 15, which was transformed in warm conc. H_2SO_4 to the aldehyde hydrate 16, analogous to 9. Attempted Schiff base formation of 16 with NH_3 gave rise to, as in the case of either 9 or 7, the ammonia adduct 16a.

Either the aldehyde 7 or its hydrate 9 underwent ready $NaBH_4$ reduction giving rise to the 2-hydroxyethyl quinazolone 17 which was also prepared in a direct manner by alkylation of 2 via its conjugate base with 2-bromoethanol. Compound 17 was further characterised as its acetate 18.

As predicted, based on the mechanism of nitroethylation of amines, compound 2 underwent smooth nitroethylation to the 2'-nitroethylquinazolone 19. Attempted transformation of 19 via the 'Nef' reaction to the aldehyde 7 or the hydrate 9 did not succeed although the nitronate salt could be obtained in good yields. The nitroethyl compound 19 was converted to 3-(2'-aminobenzoyl-3,4-dihydro-4-oxoquinazoline (22), a useful intermediate for further transformations along the cycle, via reduction to the dihydrochloride 21 followed by benzoylation.

Alkylation of 2 with 1,2-dibromoethane gave in good yields the 2'-bromethyl compound 27, which was transformed with aniline to the desired appropriately functionalised N^3-alkylated product 28 in excellent yield.

The conjugate base of 2 underwent ready Michael addition with acrylonitrile to give the 2'-cyanoethylquinazolone 33. Interestingly, the reaction of 2 with acrolein in presence of triethylamine gave the expected aldehyde 24, which is homologous to 7 and the tricyclic system 23 as an equilibrating composite in the ratio 1:3. The tendency of 24 to exist in equilibrium with the cyclic isomer 23 is in agreement with the behaviour of such systems, already exemplified with 9, 11 and 12 (vide supra).

The reaction of 2 with hydrazine gave the N^3-amino compound 29 which was transformed to the N-benzoyl derivative 31 with benzoyl chloride and with acetic formic anhydride to 30. Compounds 31 and 30 can be placed in the cycle leading to the formation of daughter oxadiazoles and the parent anthranilic acid.

Interestingly, treatment of 6-nitroquinazolone 3 with hydrazine gave in addition to the expected N-amino compound 32, a small yield of the hydrazone 33 whose formation is a reflection of the increased electrophilic nature of the 4-oxo function arising from ring nitro group substitution.

Parallel studies with the real template related to the ATP-Imidazole Cycle, namely, 5-aminoimidazole-4-carboxamide, involved the initial transformation of this to either hypoxanthine (34) or adenine (68). In either of these cases the

imidazole ring had to be protected prior to further endeavours concerning specific N^1-alkylation. Reaction of hypoxanthine 34 with $POCl_3$ gave 6-chloropurine (35), which on benzylation with benzylchloride gave an easily separable mixture of the desired 9-benzyl-6-chloropurine (36) and the isomeric 7-benzyl-6-chloropurine (37). Both 36 and 37 were transformed to the O-allyl ethers 38 and 39 *via* reaction with CH_2=CH-CH_2-ONa. 6-chloropurine (35) could be regioselectively protected at the 9-position leading to 9-tetrahydropyranyl-6-chloropurine (41) which was converted to the O-allyl ether 42. It was observed that the [3,3] transformation of the 9-benzyl-6-allyloxy purine (38) gave the expected specifically N^1-alkylated benzylhypoxanthine 40 in good yields. In contrast, similar transformation of either 39 or 42 was complex.

The structure of the N^1-allyl hypoxanthine arising from the [3,3] rearrangement of 38 was confirmed by direct alkylation of the conjugate base of 9-benzylhypoxanthine 43 with allylbromide. The 9-benzylhypoxanthine 43 was, in turn, prepared by hydrolysis of 36 under very carefully controlled conditions. Compound 43 has been demonstrated as a useful substrate for the preparation of specifically N^1-alkylated compounds of relevance to the ATP-Imidazole Cycle by reaction with $BrCH_2CH(OEt)_2$ in HMPA to the acetal 44. As was observed with 8, compound 44 could be transformed to the corresponding aldehyde 45, that existed

predominately as the "hydrate", with conc. H_2SO_4. Attempted Schiff base formation of 45 or its hydrate with dry NH_3 gave the tricyclic system 46, similar to that in the 7 → 11 change.

The reaction of 9-benzylhypoxanthine (43) with benzylbromide gave the specifically N-alkylated, 1,9-dibenzyl compound 72. Thus, this procedure could be used for the preparation of appropriately N^1-substituted hypoxanthines that could be further transformed into benzohetrocycles by the template strategy. Similarly, the reaction of 43 with 2-bromoethanol gave the 2'-hydroxyethyl alkylated compound 73

Adenine (68) was specifically alkylated to 9-benzyladenine (69). Reaction of 69 with ethylene bromohydrin gave, rather than the expected regioselectively alkylated salt that could be further transformed hydrolytically to the template amide, as in the ATP-Imidazole Cycle, the neutral, specifically N^1-alkylated imino compound 71. The benzylation of 69 was carried out under a variety of conditions using benzylbromide. In every case a neutral compound 70, similar to 71 was obtained. This basic difference in the alkylation of adenines between the *in vivo* situation leading to a salt and *in vitro* experience that gives rise to neutral imino compounds would require a different strategy for the rupture of the 1-6 bond of this system, which is crucial to the generation of the parent template. This could be achieved

with the neutral systems such as 70 and 71 by fragmentation *via* an appropriately placed leaving group at the 1'-position, leading to a nitrile, as the amide equivalent of the template.

With the preparation of a variety of specifically and appropriately substituted ligand systems belonging to the quinazolines and purines - the objective of the first phase - endeavours were initiated to further transform these compounds along the cycle *via* strategy outlined earlier, namely, a combination of sequences that necessarily would involve cyclisation and hydrolytic rupture. (*vide supra*). Based on pKa considerations a set of such 3-substituted systems were considered to be appropriate for the processing by sequence, cyclisation of the ligand conjugate base to a tricyclic system, followed by hydrolytic rupture and another set where it was felt that it would be advantageous to effect the cleavage first and cyclisation later.

The reaction of 3-allyl-3,4-dihydro-4-oxoquinazoline with PhLi followed by aqueous workup gave the PhLi adduct 54 and a small yield of 2-amino-N-allylbenzamide (55). It was further demonstrated that 54 is readily transformed to 55 by brief heating followed by work up. The ready formation of 54 is noteworthy, not only because it is a novel finding but also because it demonstrates that the aminoacetal functionality present in such adducts are quite stable. To promote cyclisation over the addition to the 1-2 bond which accounted for the formation of 54 from 6,

compound 6 was converted to the acetyl salt 47. Reaction of 47 with MeLi gave the open structure 48, again arising from addition of elements of MeLi to the 1-2 bond. Reaction of 47 with NaH, which is a strong base, at the same time a very ineffective nucleophile, gave, in very good yields, the amide 49, arising out of a sequence of reactions. Reaction of 47 with MeMgI gave none of the 1-2 adducts encountered with organolithium reagents, but compound 60 which is a ligand π isomer of 6. The isolation of compounds 49 and 50 that involve the isomerisation of the terminal π of the starting 47 to an internal one, provides proof for the formation of the expected conjugate base of 47. The trimethylsilyl salt 51 prepared in good yields from 6, gave on reaction with BuLi, the cyclic adduct 52 and the open isomer 53, which are similar to that obtained by reaction of 6 with PhLi, namely 54 and 55. It is quite possible that the ready de-silylation of 51 $\rightarrow$ 6 takes place under the conditions of the reaction prior to the interaction with the organolithium reagent. Studies with 6 and its salts 47 and 51 have brought out the great tendency of electron excess reagents to add to the 1-2 bond of quinazolones and the tendency of such systems for ready rupture. Consequently, in this series, although the expected sequence of reactions, namely, conjugate base formation and cyclisation could have occurred, the products being in equilibrium with the open presursors, such tricyclic systems perhaps were not encountered

because of the ready removal of 6 and its salts *via* nucleophilic addition followed by ring rupture.

3-(2'-hydroxyethyl)-3,4-dihydro-4-oxoquinazoline (17) was chosen as a probe to test this conclusion. Reaction of 17 with either PhLi or n-BuLi gave the adducts 56 and 57. It is concluded therefore that the reaction of 17 with the organometallic compounds must have resulted in the formation of the expected ligand conjugate base, which, on the basis of the demonstrated electrophilic character of the 1-2 bond must have cyclised to give the expected tricyclic system, as the conjugate base of the anticipated product. The formation of 56 and 57 then can only be rationalised on the basis of equilibrium involving the conjugate base of 17 and that derived from the cyclisation, this situation being disturbed by the irreversible removal of 17 by addition of the organometallic reagent, which acts as the external nucleophile.

The Michael adduct 26 offers multifacetted opportunities for interaction with PhLi. The latter, as a nucleophile, can add to either the nitrile function, that could undergo cyclisation to the 1-2 bond or add to the 1-2 bond of the quinazolone system in 26. The organometallic compound can act also as a base to form the conjugate base of 26 that again could undergo cyclo-addition or retro-Michael reaction. In the event, the reaction of 26 with PhLi gave as the major product 2 arising from a retro-Michael process. The reaction also gave, in modest yields, the PhLi

adduct 59, arising from prior nucleophilic addition to the 1-2 bond followed by retro-Michael reaction.

pKa considerations favoured the 2'-anilinoethyl quinazolone 28 as a proper substrate for cyclisation leading to tricyclic compounds of relevence to the cycle. In the event, reaction of 28, with *in situ* generated Li-di-n-butylamide gave a mixture from which a modest yield of the open product 58 could be isolated. The formation of 58 again demonstrates, that although the expected cyclisation may have been favoured, as a consequence of its being in equilibrium, the overall reaction took a different course *via* removing the substrate by addition of an external nucleophile, followed by rupture.

The 3-substituted quinazolones were endeavoured to be placed in the cycle *via* initial hydrolysis followed by cyclisation and rupture. It may be noted that the initial adduct arising from hydroxide and the 1-2 bond of quinazolone could, being symmetrically placed between two nitrogens, rupture by two pathways that could result in the attachment of the nascent formyl unit either to the 1st or the 3rd nitrogen atom. With respect to further reactions in the cycle, such a cleavage has to take place at the 1-2 site leading to the attachment of the formyl unit to the 3-nitrogen. The point of concern is that such systems, necessarily being bis amides are expected to be quite prone to further hydrolysis that may result in the loss of

this ligand. Finally, the products of hydrolysis of the 1-2 bond could be processed along the cycle *via* further cyclisation.

The reaction of 3-allyl-3,4-dihydro-4-oxoquinazoline 6 with dil. alkali followed by benzoylation of the resulting mixture, gave the allylamide 60, the benzoxazone (61) and benzoyl anthranilic acid (65), the last two arising from the anthranilic acid formed in the reaction. Compound 60 is related to the hydrolysis product o-aminobenzoic acid allylamide, arising from hydrolytic cleavage and hydrolysis, resulting in the removal of the carbon at the second position.

Since N-formyl anthranilic acid 62 gave, under the conditions of hydrolytic cleavage described above, anthranilic acid, the formation of o-aminobenzoic acid N-allyl amide from 6 could be a result of either the 1-2 or the 2-3 bond cleavage.

The hydrolytic cleavage of 14, the 6-nitro analog of 6 was quite facile and gave rise to 5-nitroanthranilic acid in good yield.

The reaction of 2,2-diethoxyethyl-3,4-dihydroxy-4-oxoquinazoline (8) with aqueous hydroxide led to the complete disintegration of the unit to the parent model template anthranilic acid, the nitrogen functionalised ligand, namely, the diethylacetal of aminoacetaldehyde and formic acid which was not isolated.

Similar results were obtained on treatment of the 6-nitro anolog of 8, namely 15, with aqueous hydroxide.

The reaction of 2'-nitroethyl,3,4-dihydro-4-oxoquinazoline (19) with aqueous hydroxide, gave, as the only isolable product, anthranilic acid which was characterised as the benzoxazone 61.

The reaction of 3-benzoylamino-3,4-dihydro-4-oxoquinazoline (31) with aqueous alkali gave again products, none of which contained the 2-carbon unit. This reaction gave compounds 67, 66 and 1, representing various stages of hydrolysis.

The aqueous alkali cleavage of the 3-substituted 3,4-dihydro-4-oxoquinazolines has not given products that could be processed on the cycle. Also no definite conclusions could be arrived at, relating to which of the two bonds, namely, 1-2 or 2-3 undergoes the initial cleavage.

The [3,3] shift in the quinazoline and purine series was taken advantage of, for the preparation of specifically N-alkylated compounds of relevence to the cycle (vide supra). It was envisaged that such a strategy, particularly involving reactions initiated with the [3,3] shift of oxime ethers and hydrazones belonging to the quinazoline and purine series could lead to specifically N-alkylated products that can undergo further transformations, under the conditions of the reaction, along the

desired cycle, progressing even to the generation of the template and the product.

Thus, the initially formed [3,3] shift products, derivable either from the oxime ethers or hydrazones, related either to the quinazolone 2 or hypoxanthine (34), could undergo further cyclisation readily and the resulting tricyclic systems could be readily transformed to the parent templates and the daughter imidazoles. In the case of such [3,3] transformations with hydrazones, the tricyclic systems arising from cyclisation of the primary [3,3] shift, could undergo further fragmentation to the product imidazoles with the concomitant generation of the carbonyl function of the template as a nitrile equivalent. In the case of oxime ethers as well as with hydrazones, such tricyclic systems could be hydrolytically transformed to the daughter imidazoles and the templates.

The reaction of 4-chloroquinazoline (4) with the conjugate base of acetone oxime, gave the expected oxime ether 74, which underwent rearrangement on neat thermolysis giving rise to compound 75. Alternately, reaction of 4, with hydrazine gave 6-hydrazinoquinazoline 76 which was converted to hydrazone 77, with acetone. Reaction of 77 with PPA, under conditions normally employed for the Fischer-Indole cyclisations gave, 3,4-dihydro-4-oxoquinazoline and the triazole 78, arising from a deep seated rearrangement.

9-benzyl-6-chloropurine (36) was transformed to the oxime ether 79 and the hydrazine 81. The reaction of 7-benzyl-6-chloropurine (37) similarly gave the oxime ether 80. Thermolysis of these compounds gave mixtures.

Interestingly, the oxime ether 82 prepared from 6-chloro-9-tetrahydropyranylpurine (41) on thermolysis gave the hypoxanthine 83.

The known tricyclic system 88 was prepared by a route so chartered, that, its acquisition and subsequent changes would constitute yet another strategy for the chemical simulation of the ATP-Imidazole Cycle, with the anthranilic acid as the model parent template.

In this approach the parent template anthranilic acid was transformed with KCNO to 84, and then to 2,4-dichloroquinazoline 85. Reaction of 85 with ethylene chlorohydrin gave the 2'-chloroethylether 86 which on mere distillation rearranged, regioselectively, to 3-(2'-chloroethyl)-2-chloro-3,4-dihydro-4-oxoquinazoline 87. Parenthetically, the 86 → 87 change involves the displacement of halogen followed by its re-acceptance at the alternate location. This transformation can, in principle, be used for the synthesis of a variety of N^3-substituted quinazolines. Reaction of 87 with aniline gave the tricyclic system 88 in good yields.

The placement of 88 in the cycle leading to the formation of N-phenylimidazoline and parent anthranilic acid, would require the reduction of the 1-2 bond of the quinazoline moiety. Attempted reduction of the 1-2 bond of the quinazoline moiety of 88, which is highly electron rich by virtue of attachment of the 2-centre to three nitrogen atoms, was found to be extremely difficult. Forcing conditions such as with $NaBH_4/AlCl_3$ in hot diglyme, gave product 89 arising from the loss of the 4-oxo function. Addition of nucleophiles to 88 also did not succeed. Treatment of 88 with PhLi gave the interesting tricyclic compound 90. The contribution of the N-phenyl moiety to the difficulty in the reduction has been demonstrated. Thus, whereas the trimethylsilyl salt 92 prepared from 88 could not be reduced with $NaBH_4$, compound 51, arising from 6 gave a good yield of the reduced product 91.

In the present work, the objectives with reference to the first stage, namely, the preparation of a variety of suitable specifically N-alkylated systems affixed to either the template or the model template has been, by and large, accomplished. The second stage, relating to the further transformations of such systems to the daughter products with the regeneration of the templates, could not be solved. However, these investigations have brought out quite clearly subtle facets associated with the chemistry of quinazolines and purines. In the case of quinazolines, the highly electrophilic nature of the 1-2 bond, that

provided a pathway for the removal of the tricyclic systems that existed in equilibrium, made cyclisation studies infructuous. The present work has shown that the conditions for the successful cyclisation is delicately poised and it has helped to define circumstances, where such a cyclisation can take place. The hydrolytic cleavage studies of the N^3-substituted quinazolines gave invariably products where the 2-carbon of the parent was removed. It can be concluded that the scission of the 4-oxo grouping would be more attractive, compared to addition to the 1-2 bond and this may be achieved by blocking the 2-position by substitution. Both in the case of hypoxanthine and adenine, related to the parent template, and in the case of quinazoline 2 related to the model template, the cleavage of respectively, either the 1-6 bond or the 3-4 bond could be brought about by hydrolysis or by fragmentation. Studies with adenine has shown that the latter strategy could be quite promising.

In sum, the present work has enabled the construction of a broad based strategic frame work, that would eventually pave the way for the realisation of the solution relating to the chemical simulation of the salient features of the ATP-Imidazole Cycle.

CONTENTS

****

A. INTRODUCTION

The strategies used in nature relating to the construction of a variety of molecules should reflect the consequences of evolution and experiences covering a span of a number of years. In sharp contrast, the *in vitro* synthesis of diverse organic compounds is an area that is often goal oriented and much of the developments in this area took place in the preceding five decades. Consequently, the art in biosynthesis, often, is an example of a very high degree of sophistication in the art of organic synthesis. The chemical simulation of such processes therefore would lead to the addition of a new dimension to synthetic procedures and would make synthetic operations more elegant and more economical. Of particular interest is the fact that vital synthetic operations related to life, proceed by cyclic pathways. Thus, the transformation of carbondioxide to sugars - Calvin Cycle - takes place by a cyclic pathway involving a pentose. The Kreb's cycle, centrally associated with carbohydrate metabolism as well as with the bio-synthesis of a variety of essential substances, proceeds by a cyclic operation. The Urea cycle is another elegant illustration of nature's strategy where

two cyclic operations act in concert. The choice by nature to use cyclic pathways exemplifies a high degree of evolution in organic synthesis, since, such a strategy offers more advantages with reference to yields, versatility and efficiency. Even amongst such elegant cyclic operations pertaining to biosynthesis, the ATP-Imidazole Cycle should be considered unique, since, it is not only associated with the biosynthesis of histidine but also ATP and GTP, that enable the maintenance of life systems at the required high potential. In addition, this cyclic process illustrates the formation of a daughter imidazole molecule on a parent imidazole template. The details relating to this have been presented in Section B.

The present work is an endeavour to chemically simulate the salient features of the ATP-Imidazole Cycle.

B. BACKGROUND

THE ATP-IMIDAZOLE CYCLE:

Template mediated reactions in life processes, by and large, take place in 2 phase media where the operating part of the system is incorporated on a polymer backbone. A unique exception to this feature is the ATP-Imidazole Cycle - related to the biosynthesis of ATP, GTP and histidine - wherein a mobile, monomeric imidazole acts as a template to produce a daughter imidazole. The pathways by which this cyclic event takes place became known as a result of extensive and painstaking experiments. The salient features of the ATP-Imidazole Cycle are illustrated in CHART B.1.

A cyclic operation can be defined as a process where the starting material in the first step becomes product of the last step. In the case of the ATP-Imidazole Cycle, the synthesis of the daughter product is initiated with 5-amino-1-ribosyl-4-imidazole-carboxamide-5'-phosphate (1). In the last step, in addition to the regeneration of 1, imidazoleglycerol phosphate (2) is formed which is restructured in subsequent processes to histidine.

The overall process essentially involves the use of the proximately aligned NH_2, $CONH_2$ groupings in 1 to generate, sequentially, the hypoxanthine ring system 3, the adenine 4, the specifically 1-alkylated phosphoribosyl ATP (5), phosphoribosyl AMP (6), the ring ruptured phosphoribosyl formimino-1-(5'-phosphoribosyl)-4-imidazolecarboxamide (7), the Amadori rearrangement product phosphoribulosyl formimino-5-amino-1-(5'-phosphoribosyl)-4-imidazole carboxamide (8), which on amination with glutamine, followed by cyclisation and rupture leads to 1 and 2 (CHART B.1).

The strategy involved in the above cycle can be abstracted as shown in CHART B.2, from which it is obvious that only a single nitrogen from 1 appears in the daughter product.

The bio-synthesis of the template 1, as presented in CHART B.3, proceeds from phosphoribosyl pyrophosphate (9) *via* sequence-amination to 5-phosphoribosyl amine (10), amide formation with glycine to 11, specific N-formylation to N-formyl glycinamide ribonucleotide (12), amination with glutamine to 13, cyclisation to 5-aminoimidazole ribonucleotide (14), which then undergoes an unusual orthocarboxylation with CO_2 to give 15, which undergoes amidation with aspartic acid giving rise to 1. The daughter product from the cycle, namely, imidazole glycerol phosphate (2) is transformed to histidine (16) through intermediates, imidazole acetol phosphate (17), histidinol phosphate (18), histidinol (19) and histidinal (20) (CHART B.4).

CHART B.1

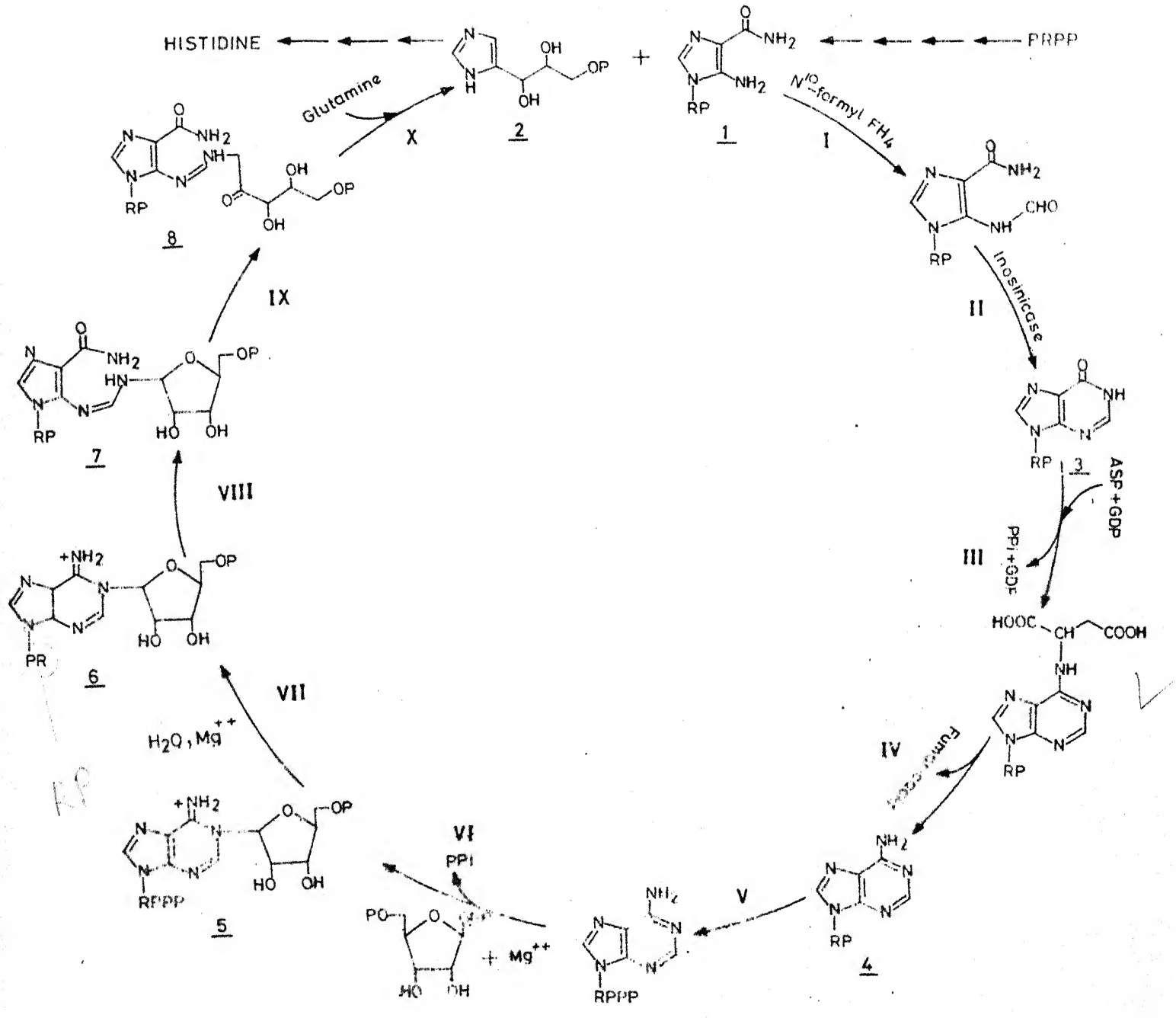

HISTIDINE
PRPP
Glutamine
X
2
1
N^{10}-formyl FH_4
I
8
II
Inosinicase
IX
7
3
ASP+GDP
III
VIII
6
IV
Fumarase
VII
H_2O, Mg^{++}
5
VI
PPi
+ Mg^{++}
V
4
RP
RPPP

CHART B.2

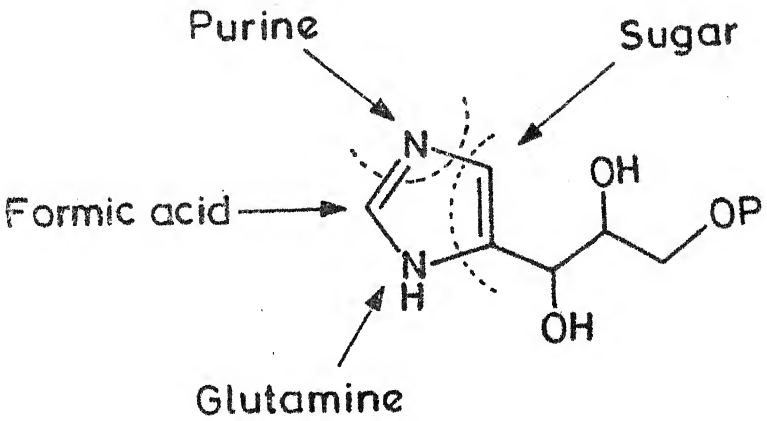


CHART B.3

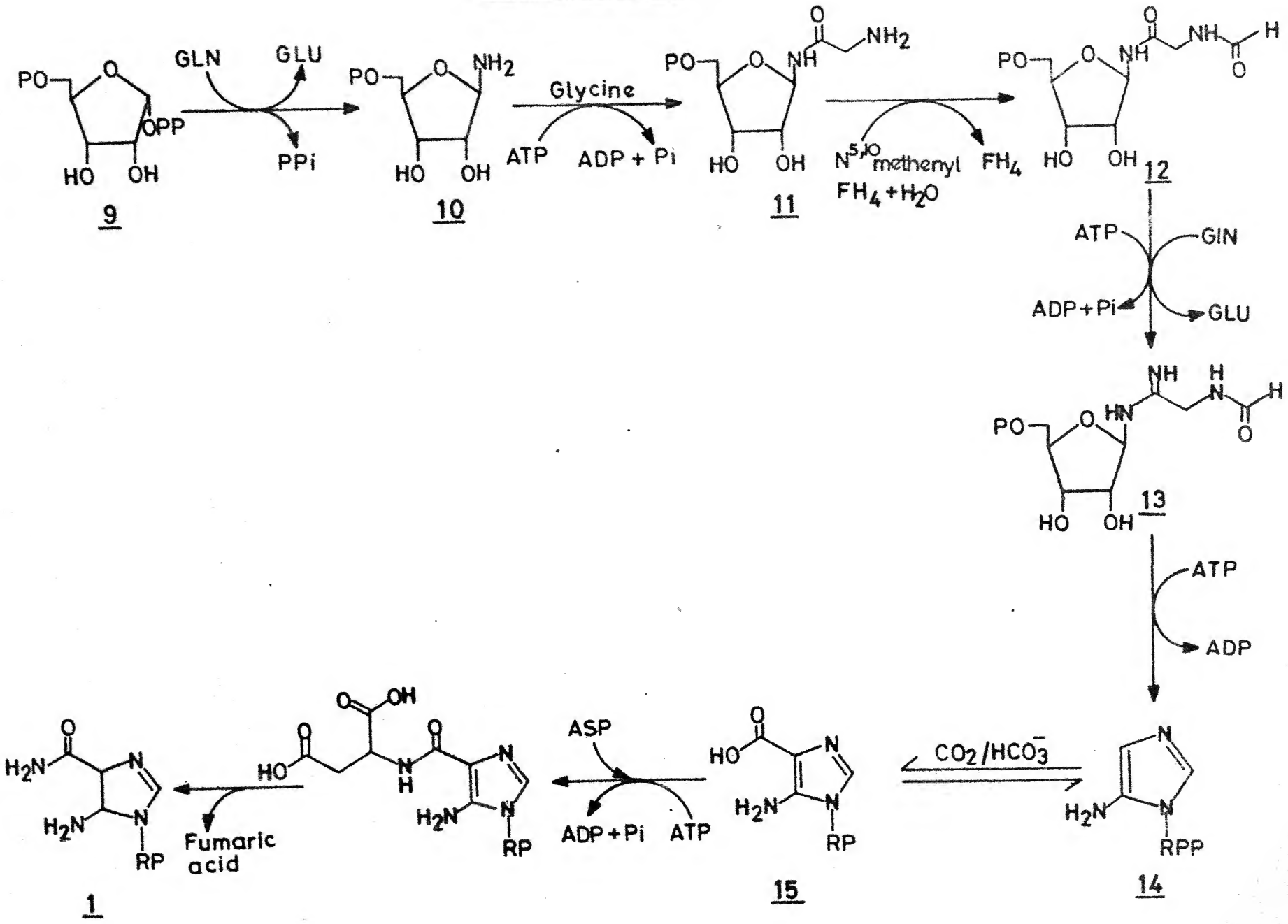
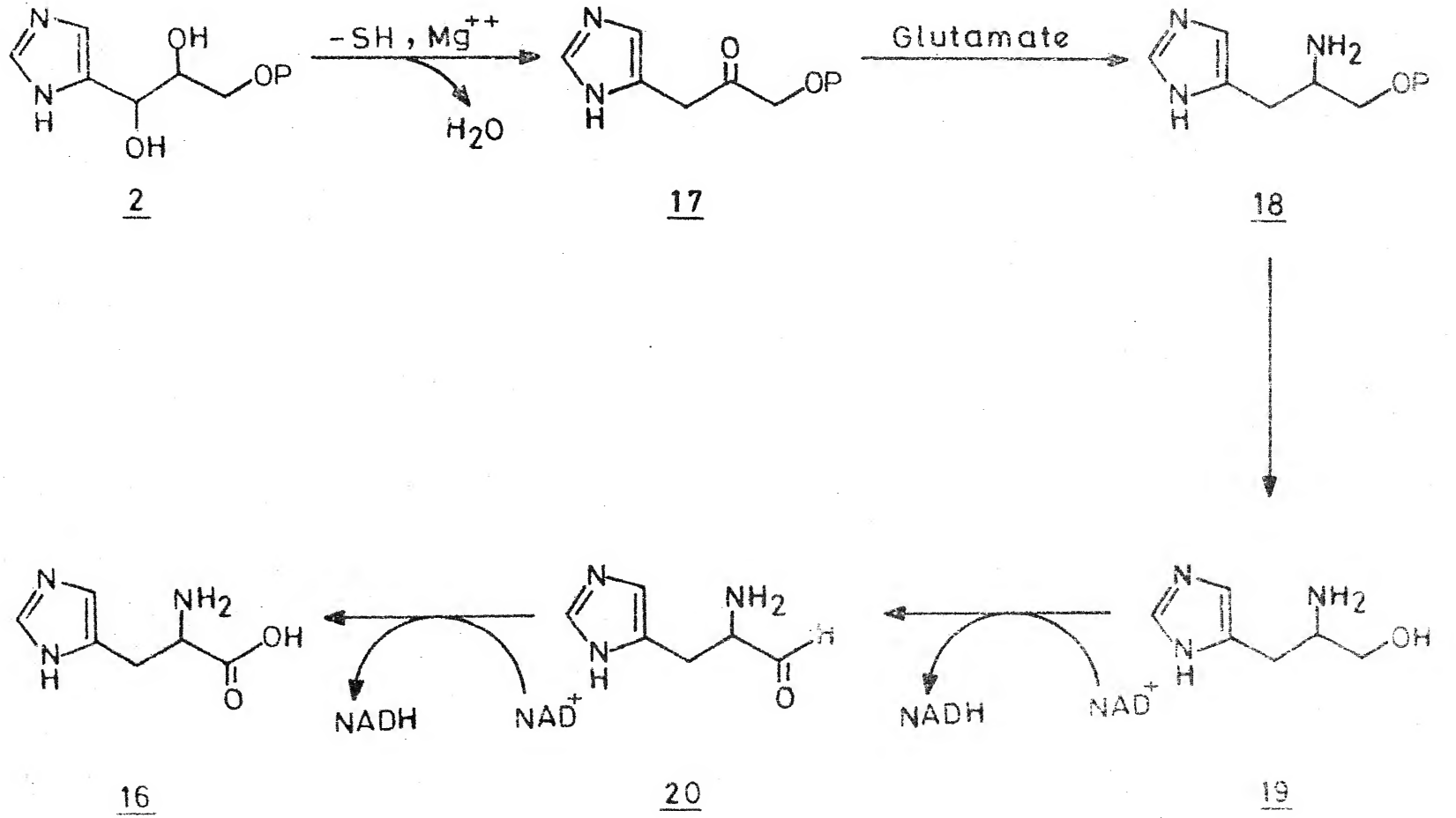

PO
OPP
HO OH
9
GLN
GLU
PPi
NH2
10
Glycine
ATP
ADP + Pi
NH2
O
NH
11
N5,10 methenyl FH4
FH4 + H2O
12
ATP
GIN
ADP+Pi
GLU
NH
H
HN
13
ATP
ADP
CO2/HCO3−
RPP
14
ASP
ADP+Pi
ATP
15
Fumaric acid
1
RP

CHART . B . 4



Details pertaining to the delineation of pathways outlined above, form the remaining part of the section.

Biosynthesis of 5-amino-1-ribosyl-4-imidazolecarboxamide-5'-phosphate (1)

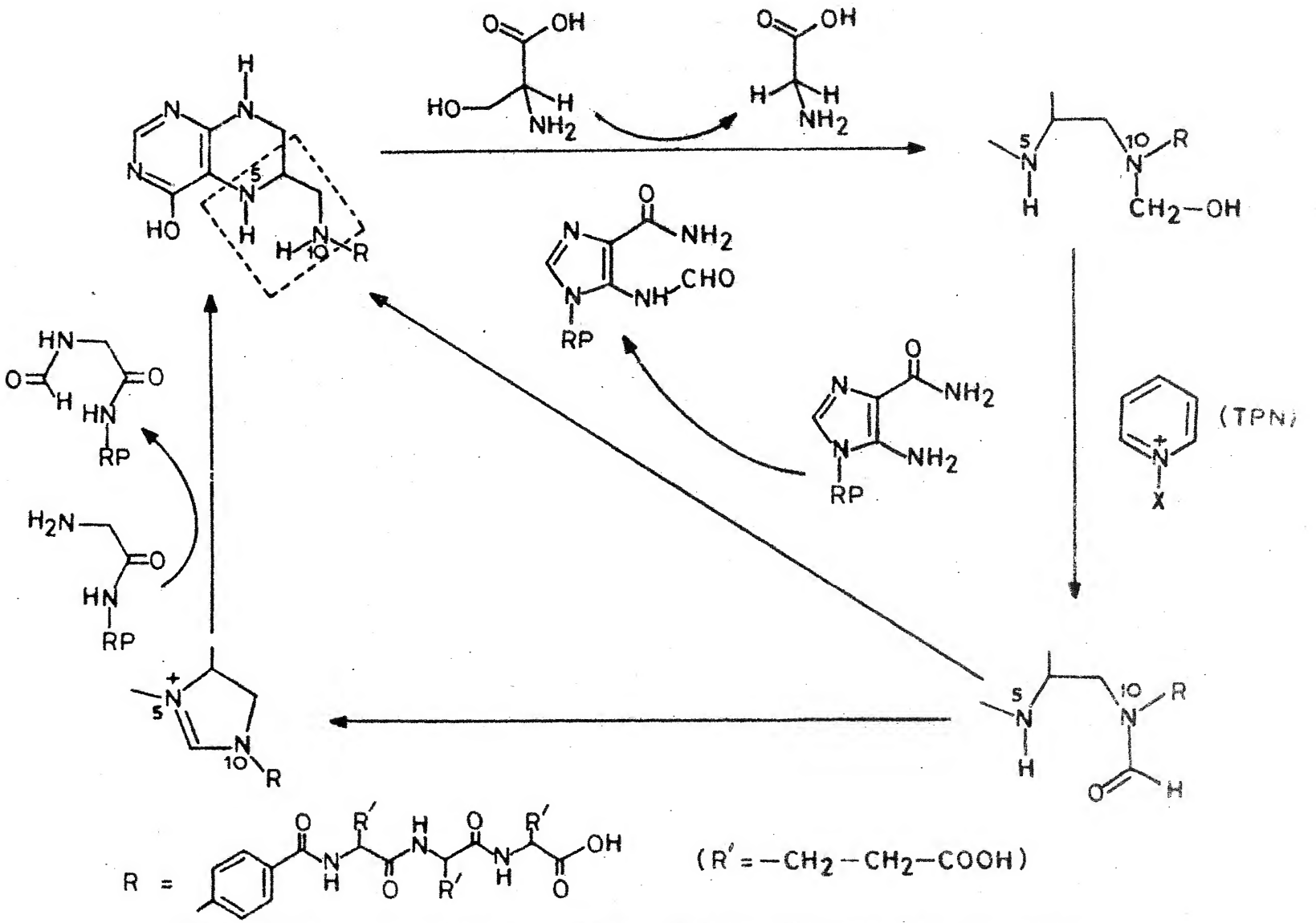
The primary reaction in the de novo synthesis of purines is the replacement of the 1-pyrophosphate moiety of phosphoribosyl pyrophosphate (9) with an amino group leading to 10. As anticipated on the basis of a nucleophilic displacement process, the incoming amino function takes up the β-configuration. Compound 10 being hemi-aminoacetal, is quite unstable and the propensity for the rupture of the furanose ring should be curbed by acylation of this unit, which is accomplished with glycine leading to 11. Studies have shown that the enzyme that promotes the 9 to 10 change is a single compound and the process is believed to be essentially irreversible. The acylation process involved in 10 ⟶ 11 change is catalysed by enzyme that requires ATP activation. Parenthetically, the acylation reaction has been demonstrated to be reversible.[1-3] Compound 11 is formylated in the presence of the coenzyme, N^5,N^{10}-anhydroformyl tetrahydrofolic acid, to the N-formyl compound 12. The enzyme catalysing this reaction has been purified and the process is greatly enhanced in the presence of Mg^{2+} and ribose-1-phosphate.[4,5]

The template 1 consists of two ring nitrogens as part of the imidazole system. The reaction outlined above have led to the introduction of these, starting from 9. The remaining two nitrogens, namely, those present in the 5-amino group and the 4-carboxamide are incorporated subsequently. The 5-amino group is introduced *via* transformations of the acetamide 12 to the corresponding amidine 13 with glutamine. This reaction, as anticipated, requires ATP activation.[6] The open chain unit, sequentially thus constructed from 10, is cyclised to an imidazole involving ATP activation leading to 5-amino imidazole-ribonucleotide 14.[6] In the next step, the enamine unit present in 14 accepts elements of CO_2 leading to the introduction of the 4-carboxylic acid unit. The incorporation of CO_2 has been established by labelling experiments and the enzyme involved has been partially purified.[7] The transformation of the carboxylic acid function in 15 to the amide 1 is accomplished by ATP mediated amide formation with aspartic acid, followed by fumaric acid elimination. Each of these steps are catalysed by different enzymes and it is possible to isolate the intermediate amide. Interestingly, the two enzymes involved coexist and it has been shown that either of the enzymes is devoid of any activity in the reaction catalysed by the other.[8,9] The template amide 1 thus constructed (CHART B.3) now enters the ATP-Imidazole Cycle (CHART B.1).

The first step in the ATP-Imidazole Cycle is the formylation of the 4-amino function which is again brought about by N^{10}-formyl tetrahydrofolic acid. A trans-formylase catalyses this reaction but it has been thus far proved difficult to separate this from the enzyme inosinicase, which is involved in the step II of the cycle. Two folic acid mediated formylations have been described thus far. Interestingly, it has been demonstrated that N^5,N^{10}-anhydroformyl tetrahydrofolic acid specifically donated its formyl group in the 11 $\longrightarrow$ 12 change (CHART B.3) and that N^{10}-formyl tetrahydrofolic acid is the immediate donor in the transformation of the template 1 to the corresponding formamide.[12,13] (CHART B.1). An integrated picture of the two transformylation reaction is presented in CHART B.5.

The step II of the cycle leading to the hypoxanthine system 3 is readily brought about by the enzyme inosinicase. Indeed, attempts to demonstrate the accumulation of the formyl precursors failed owing to its extremely ready conversion to 3.[14]

Compound 3, thus formed in step II can either be processed further in the cycle or transformed to Guanosine monophosphate (GMP), a precursor of GTP. The latter transformation requires two changes, namely, the introduction of a hydroxyl group in 2-position and its subsequent replacement by an amino group. The first step involving hydration and oxidation requires the coenzyme DPN and the enzyme Inosinic dehydrogenase. The donor



RP = Ribose phosphate ; TPN = Triphospho pyridine nucleotide.

of the amino group depends on the organism. In avian and mammalian systems, glutamine is the preferred donor, whilst in bacterial systems ammonia is selectively used. The process involves ATP activation (CHART B.6).[15-19]

The hypoxanthine 3 is further transformed in the ATP-Imidazole Cycle to AMP, the amino nitrogen being provided by aspartic acid as in the case of 15[20] (CHART B.3). Interestingly, whilst ATP activation is needed in the transformation of 3 to GMP, in the amination reaction leading to AMP, GTP activation is required !

This activation is required in the formation of the adenosine monophosphate succinate which is then cleaved to fumaric acid and AMP (4). The mechanism of the addition-elimination process, studied with labelled substrates, shows that the cleavage to 4 takes place in a trans fashion specifically leading to fumaric acid. The lack of noticeable H-isotope effect in the cleavage reaction is concluded as an indication of involvement of an intermediate.[21] Presumably the slow step is a N-protonated intermediate that can be expected to cleave very rapidly.

The transformation of AMP ⟶ ATP, the next step (V) in the cycle is accomplished by substrate level phosphorylation which is generally catalysed by kinase enzymes. The ATP thus produced is, naturally, if needed, available to the system.

CHART B.6

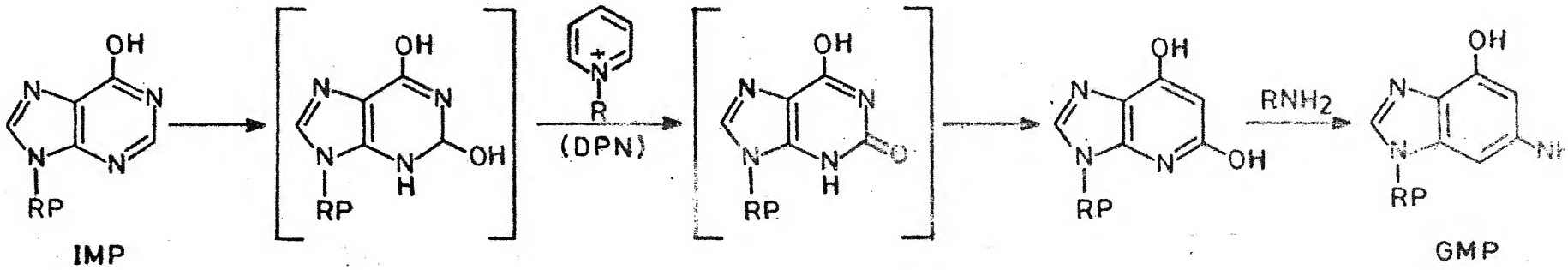
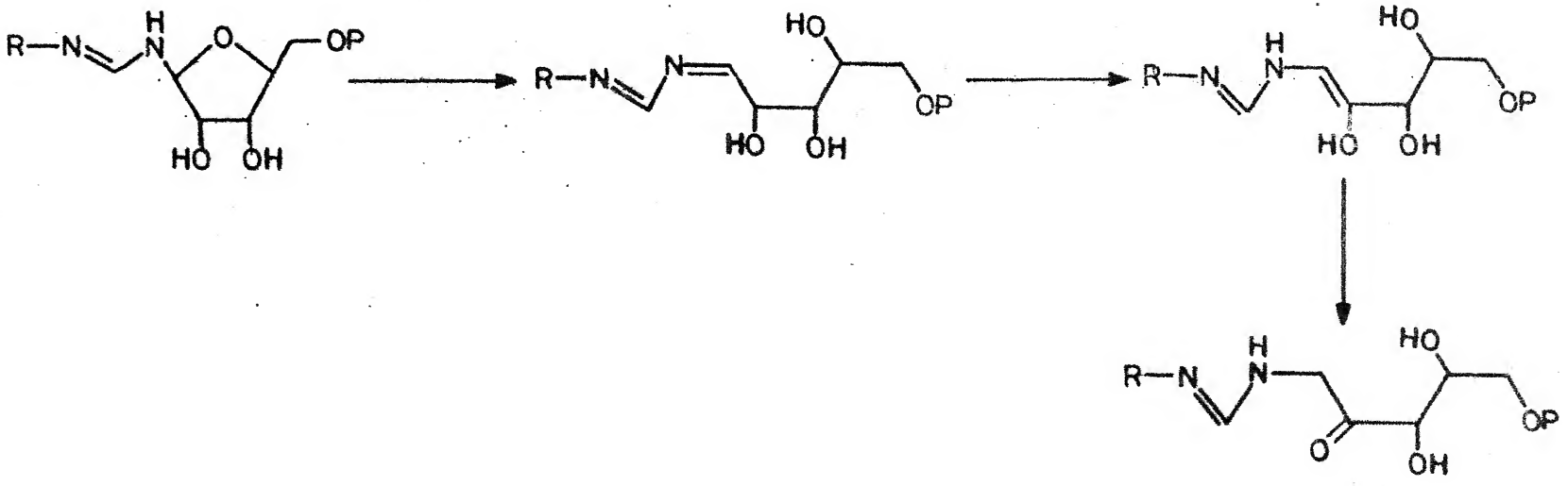


CHART B.7



Specific N-alkylation of ATP with ribose phosphate leading to the key compound 5 is mediated by the enzyme phosphoribosyl-ATP-pyrophorylase. This alkylation is reversible and is strongly inhibited by histidine.[22]

Studies with an extract of a histidine requiring mutant of salmonella typhimurium have shown that the next step in the ATP-Imidazole Cycle is the hydrolysis of 5 to phosphoribosyl AMP (6). This reaction is catalysed by the enzyme PR-AMP-pyrophosphohydrolase.

In the next step of the cycle, in compound 6, the 1-6 bond is specifically, hydrolytically cleaved, by the enzyme PR-AMP-1,6-cyclohydrolase leading to compound 7, wherein the carboxamide moiety present in template 1 is regenerated.[23]

Further insight related to the events that take place in the cycle has been obtained from investigations using extracts of depressed histidine requiring mutants of salmonella typhimurium. These endeavours have demonstrated that compound 7, undergoes a rather unusual 'Amadori' type rearrangement leading to the amidine 8.[24,25] The 7 → 8 change can be rationalised on the basis of a series of favourable 1,3 prototropic shifts as illustrated in Chart B.7.

The final step in the ATP-Imidazole Cycle, namely, the transformation of 8 ⟶ 2 + 1 is initiated with the introduction

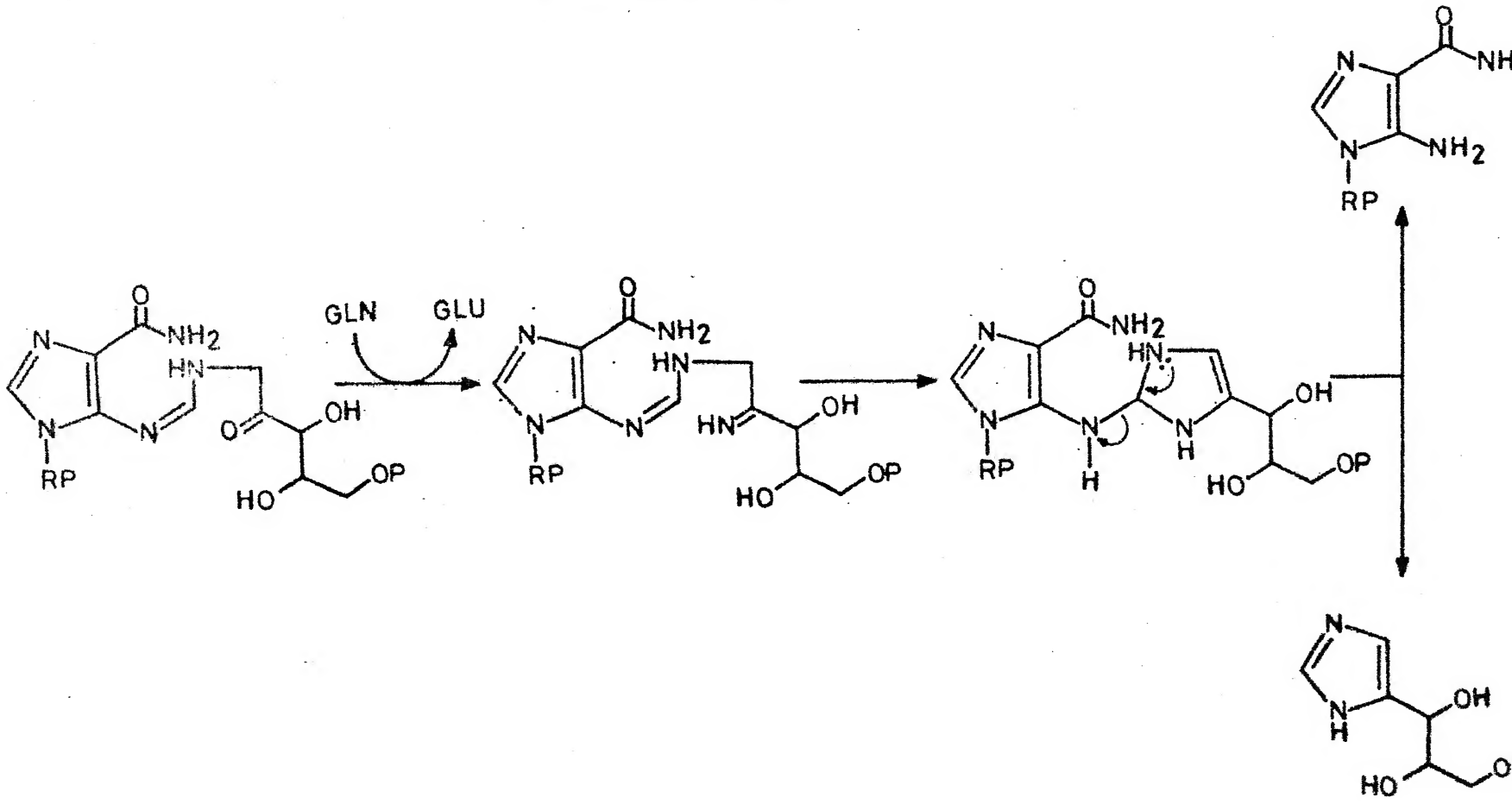
of the 1-N of 2 with glutamine, a process that requires ATP activation. The resulting imino compound undergoes facile cyclisation to an aminal which can be considered as a composite of the template imidazole 1 and the daughter product 2 attached by a fragile aminal umbilical chord whose rupture leads to the delivery of the daughter products[24,26,27] (CHART B.8).

Salient features relating to the further transformations of the daughter product 2 from the ATP-Imidazole Cycle to histidine has already been presented in CHART B.4. The first step is a specific dehydration by the enzyme de-erythroimidazole glycerol phosphate dehydrase. This enzyme has been partially purified and requires Mn^{+2} ions and a reducing agent such as mercaptoethanol for activity. The optimum pH for the 2 $\longrightarrow$ 17 change is 7.5.[28]

The trans-amination reaction on 17 leading to histidinol phosphate has been well studied. The enzyme responsible for this reaction, namely, imidazole acetol phosphate transaminase has been purified and is shown to require pyridoxal phosphate for its activity. Interestingly, the 17 $\longrightarrow$ 18 change, mediated by the above enzyme system and L-glutamic acid is effective only with the phosphate ester and not the free alcohol.[29]

Hydrolysis of the phosphate 18 to histidinol is brought about by a substrate specific hydrolytic enzyme.[30]

CHART B.8



The further transformation of histidinol to histidine has been carefully examined. The overall oxidation takes place in two stages involving histidinal as a fugitive intermediate. Both the oxidations appear to be catalysed by the same enzyme and DPN^+ is the common oxidising coenzyme.[30-32]

The above account relating to the ATP-Imidazole Cycle is a description of a most meticulously orchestrated process, wherein each of the participants, whether they are substrates, enzymes or co-enzymes, play their roles to utmost perfection. The cycle also illustrates a highly developed art of organic synthesis and it is most likely that the final details evolved over a period of time and as a result of extensive experimentation.

C. PRESENT WORK

A discussion of the research planned

The strategy of growing the daughter on the parent 5-amino-4-imidazole carboxamide can be analysed in terms of the stepwise introduction of the needed one nitrogen and three carbons, with the amide nitrogen of the parent, destined to be part of the daughter molecule. The protocol, which involves three distinct stages, as illustrated in CHART C.I, involves, 1. the introduction of the carbon bridge that connects the two nitrogen functionalities of the parent, 2. specific alkylation with $-CH_2-\overset{b}{C}=N-d$, and 3. Cyclisation with hydrolysis. Parenthetically, a cyclic strategy enables presentation of the overall change in terms of synthetic and antithetic analysis, as a composite picture. Thus, in CHART C.I, the clockwise arrows indicate the synthetic route and the anti-clockwise arrows, the antithetic analysis.

In principle, the versatility of the ATP-Imidazole Cycle can be further augmented leading to the template synthesis of a host of heterocyclic compounds as illustrated in CHART C.II. Thus, the parent imidazole pertaining to the ATP-Imidazole Cycle

(CHART C.I) can be redesignated by affixing the operating part of the cycle onto an aromatic ring, leading to anthranilic acid amide. It was anticipated that such a modification could offer several advantages compared to the reactive, multifunctional imidazole moiety that supports the operating part in the ATP-Imidazole Cycle. Interestingly, a similar set of sequences from anthranilic acid amide would necesarily involve the incorporation of the HCOOH equivalent leading to 4-oxoquinazoline. Additionally, the 3-atom backbone that is necessary in the specific alkylation can be varied, the ligands attached to it diversified, thus giving rise to the synthesis of a variety of heterocyclic systems, regenerating the parent (CHART C.II).

In the present work, it was proposed to implement the objectives in terms of the three stages referred to above. It was realised that the daughter products could be generated from the parent from the specifically alkylated first step, in a variety of ways, that could even combine the second and third stages of the cycle, either *via* a sequence involving cyclisation and rupture or by the reverse operation, namely, rupture and cyclisation. Thus, the products arising from the specific alkylations can be converted back to the template and the product molecules *via* three distinctly different pathways namely, 1. cleavage of the CO-NH as in ATP-Imidazole Cycle or 2. cyclisation to a tricyclic system or 3. regiospecific hydrolytic cleavage leading to the specific attachment of the resulting -CHO

CHART C.1

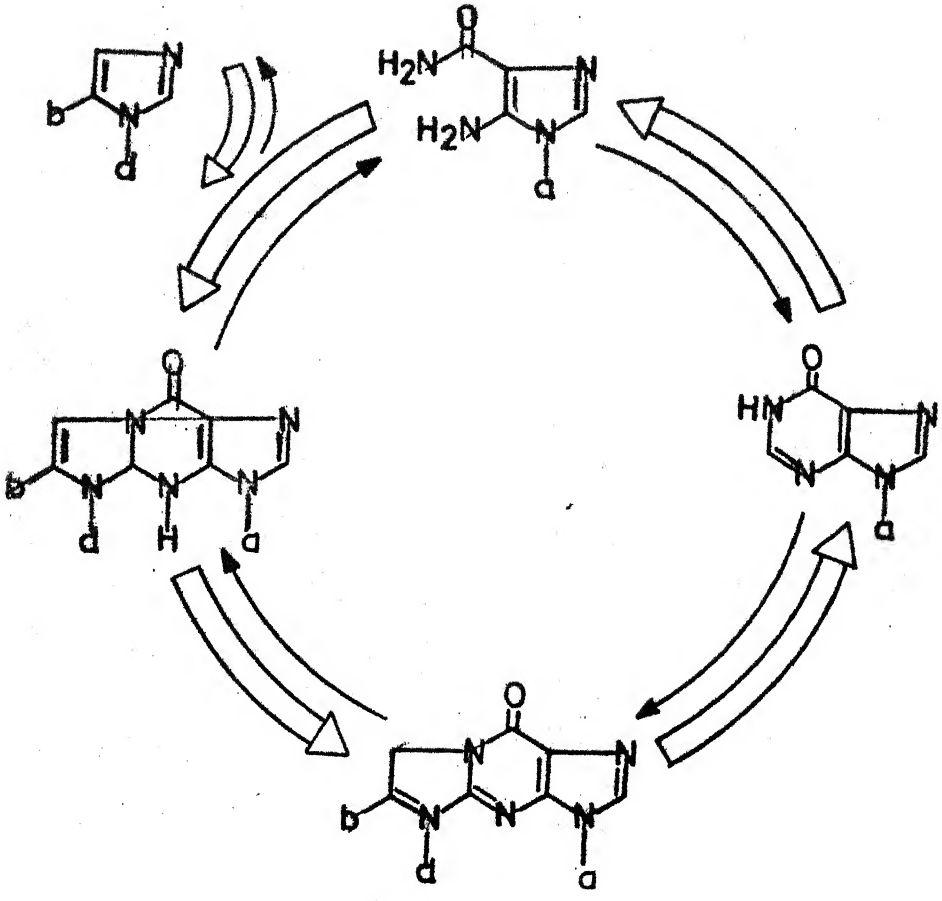
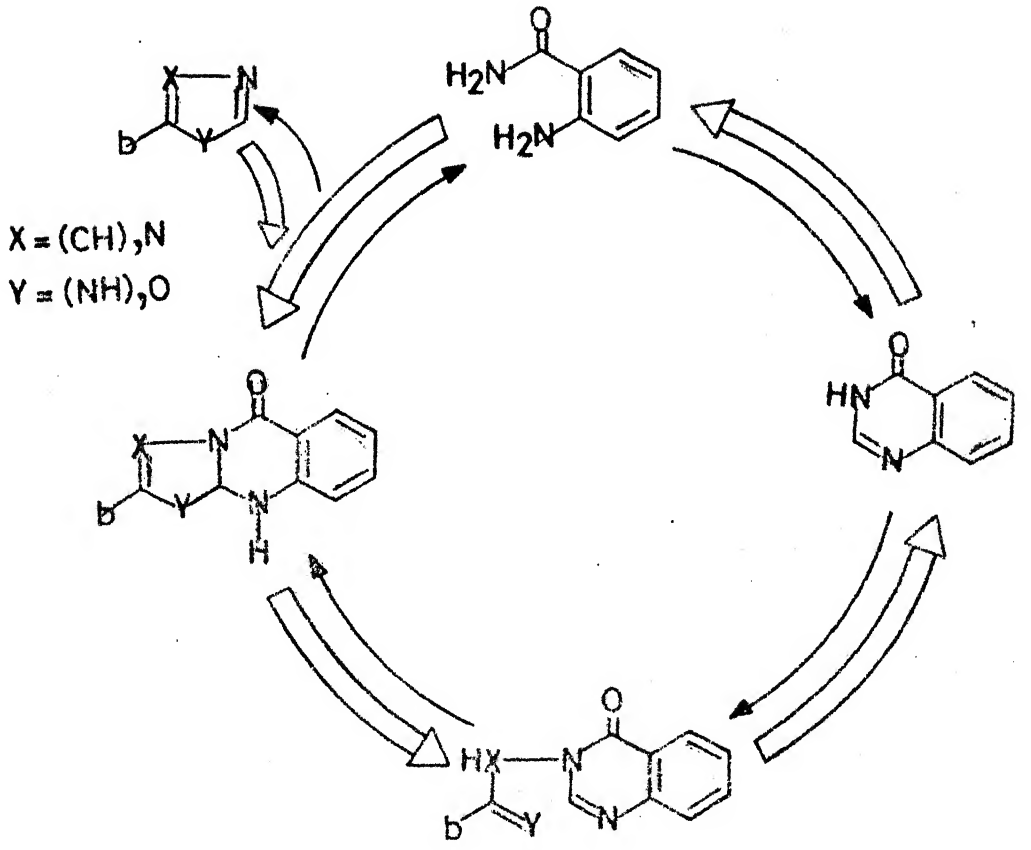


CHART C.II

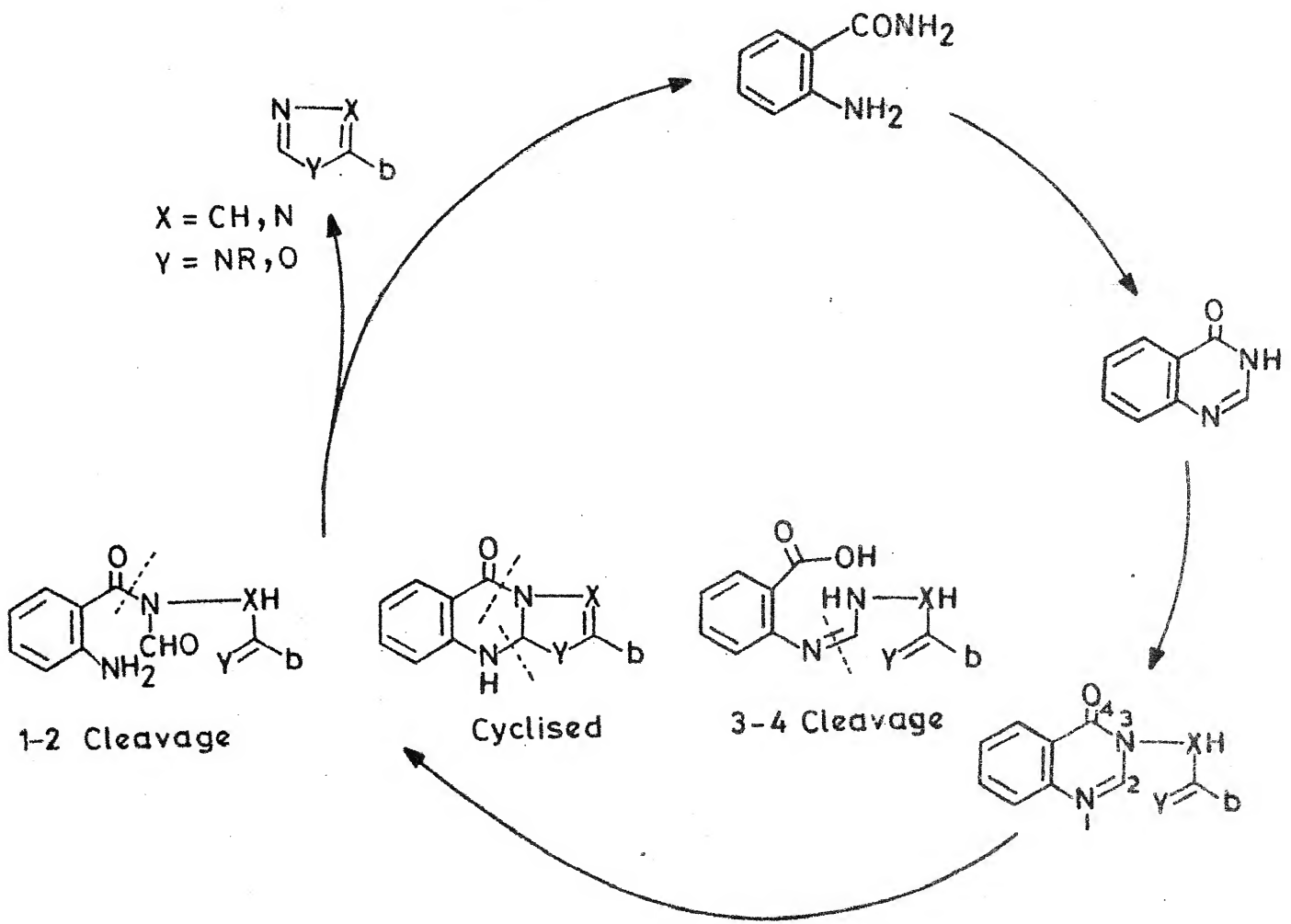


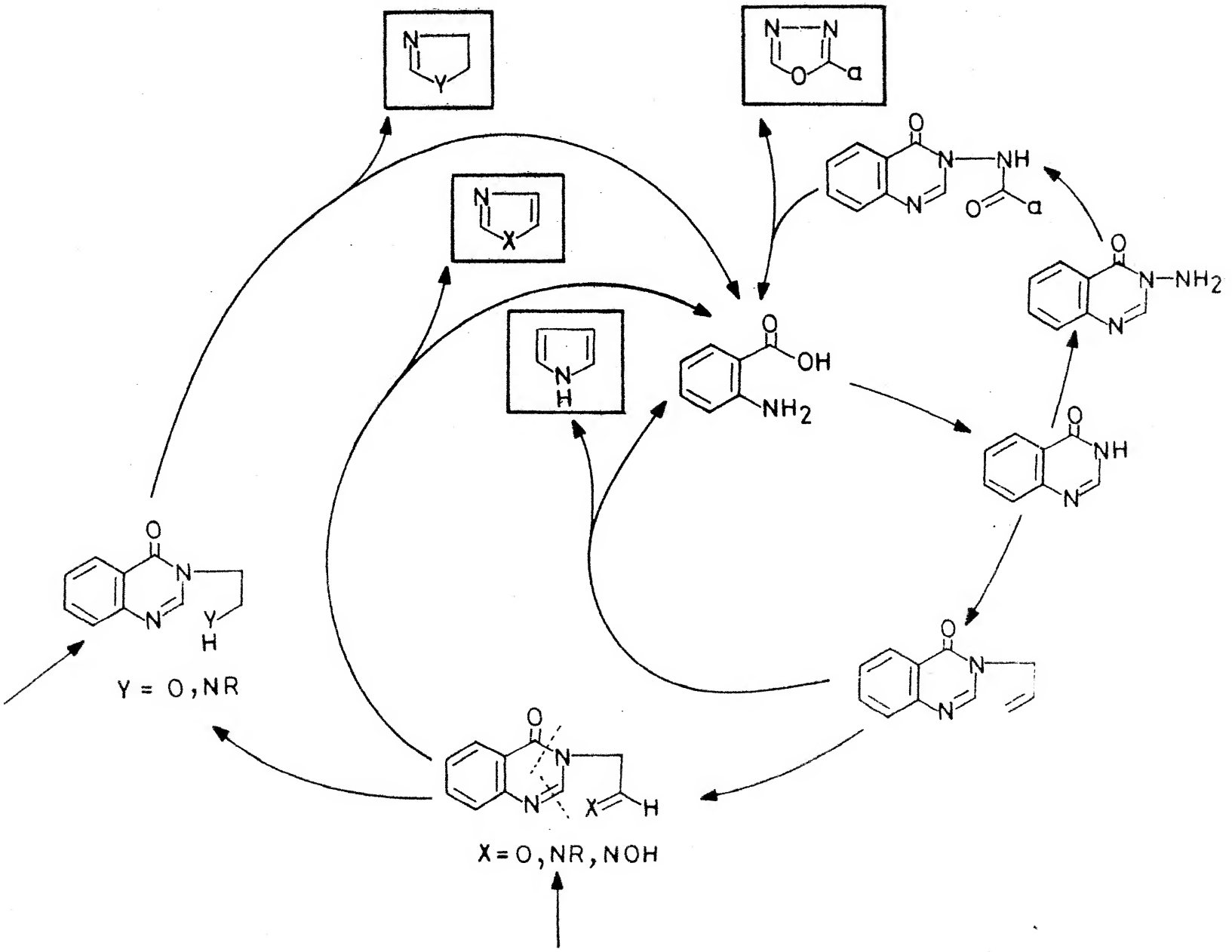
function to the amide nitrogen of the template parent. Each of these three pathways can lead to the product molecule and the parent as indicated with dotted lines in CHART C.III, either by convergent or by divergent pathways. In the present work parallel studies have been carried out using anthranilic acid or 5-aminoimidazole-4-carboxamide as the parent templates. The overall plan of work is illustrated in CHART C.IV using anthranilic acid as the parent. It was proposed to prepare the required substituents at the 3-position in order that they may be transformed to product molecules. The N^3-alkylated systems could be anticipated to lead to, *via* pathways similar to that of the ATP-Imidazole Cycle, to diverse heterocycles. Thus, the 3-allyl can lead to pyrrole, the 3-(2'-oxoethyl) to oxazole, the 3-(2'-oximinoethyl) to N-hydroxyimidazoles, the 3-(2'-iminoethyl) to imidazoles, the 3-(2'-hydroxyethyl) to oxazoline and the 3-(2'-aminoethyl) to imidazoline (CHART C.IV). In all these cases the parent anthranilic acid would be generated.

The preparation of specifically N-alkylated precursors

The present work reports results pertaining to salient features of the chemical simulation of the ATP-Imidazole Cycle *via* parallel series of experiments starting from the model system anthranilic acid and the parent relating to the ATP-Imidazole Cycle itself, namely, 5-aminoimidazole-4-carboxamide. Studies

CHART C.III


CONH2
NH2
O
NH
N
X = CH, N
Y = NR, O
1-2 Cleavage
Cyclised
3-4 Cleavage
OH
HN
XH
CHO
b


Y = O, NR
X = O, NR, NOH

were initially carried out with anthranilic acid series and then were translated to the imidazole system.

The synthesis of specifically N-alkylated quinazolines:

The nitrogen centre, that is the nucleus for the further metamorphosis to template mediated preparation of heterocyclic systems, was introduced by the incorporation of elements of formamide *via* reaction of anthranilic acid (1) and formamide. Thus an intimate mixture of anthranilic acid (1) and formamide when held at 180°C gave 3,4-dihydro-4-oxoquinazoline in 85% yield[33,34] (CHART C.1).

---

2 : mp. 216°C

ir : ν_{max}(KBr) cm^{-1}: 3200, 3170 (NH), 1700 (amide carbonyl).

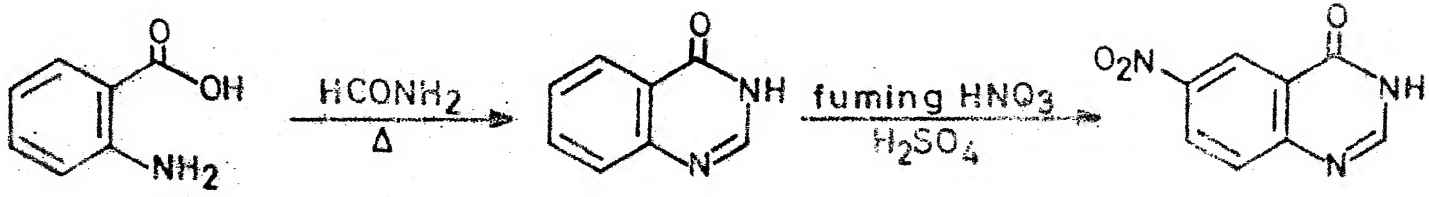
In endeavours to promote cyclisation of the specific N-alkylated quinazolones, the 6-nitro analog of 2 was prepared *via* treatment of 2 with a nitrating mixture, in excellent yields[35] (CHART C.1).

---

3 : mp. 286°C

ir : ν_{max}(KBr) cm^{-1}: 1675 (amide carbonyl), 1610, 1575 (C=C, C=N), 1510, 1350 (NO_2).

CHART.C.1



1 2 3

The specific N^3-alkylation of the quinazolone 2 was accomplished by a novel [3,3] shift. Thus, compound 2 was transformed to 4-chloroquinazoline (4) with $POCl_3$[34] which was transformed to 4-allyloxyquinazoline 5 in 80% yields *via* treatment with the conjugate base of allylalcohol. Compound 5 when thermolised under nitrogen at 200°C, for 24 hr, gave a 75% yield of the desired 3-allyl-3,4-dihydro-4-oxoquinazoline[36,37] (CHART C.2). The structural assignment for 5 and 6 is supported by spectral and analytical data. Inspite of the great interest in [3,3] rearrangement (Claisen rearrangement) such a change has not been demonstrated in the quinazoline series. Interestingly this rearrangement involves an O ⟶ N carbon migration.

---

5 : bp. 130°C/0.2 mm

ir : ν_{max}(neat) cm^{-1}: 3070, 3040 (aromatic, olefinic CH), 1620, 1570 (C=C, C=N), 1090 (C-O).

nmr: $\delta(CDCl_3)$ 60 MHz: 5.0 (m, 2H, $-O-C\underline{H}_2-CH-$), 5.2 (m, 2H, $-CH=C\underline{H}_2$), 6.1 (m, 1H, $-C\underline{H}=CH_2$), 7.25-8.5 (m, 4H, benzene ring), 8.66 (s, 1H, pyrimidine ring).

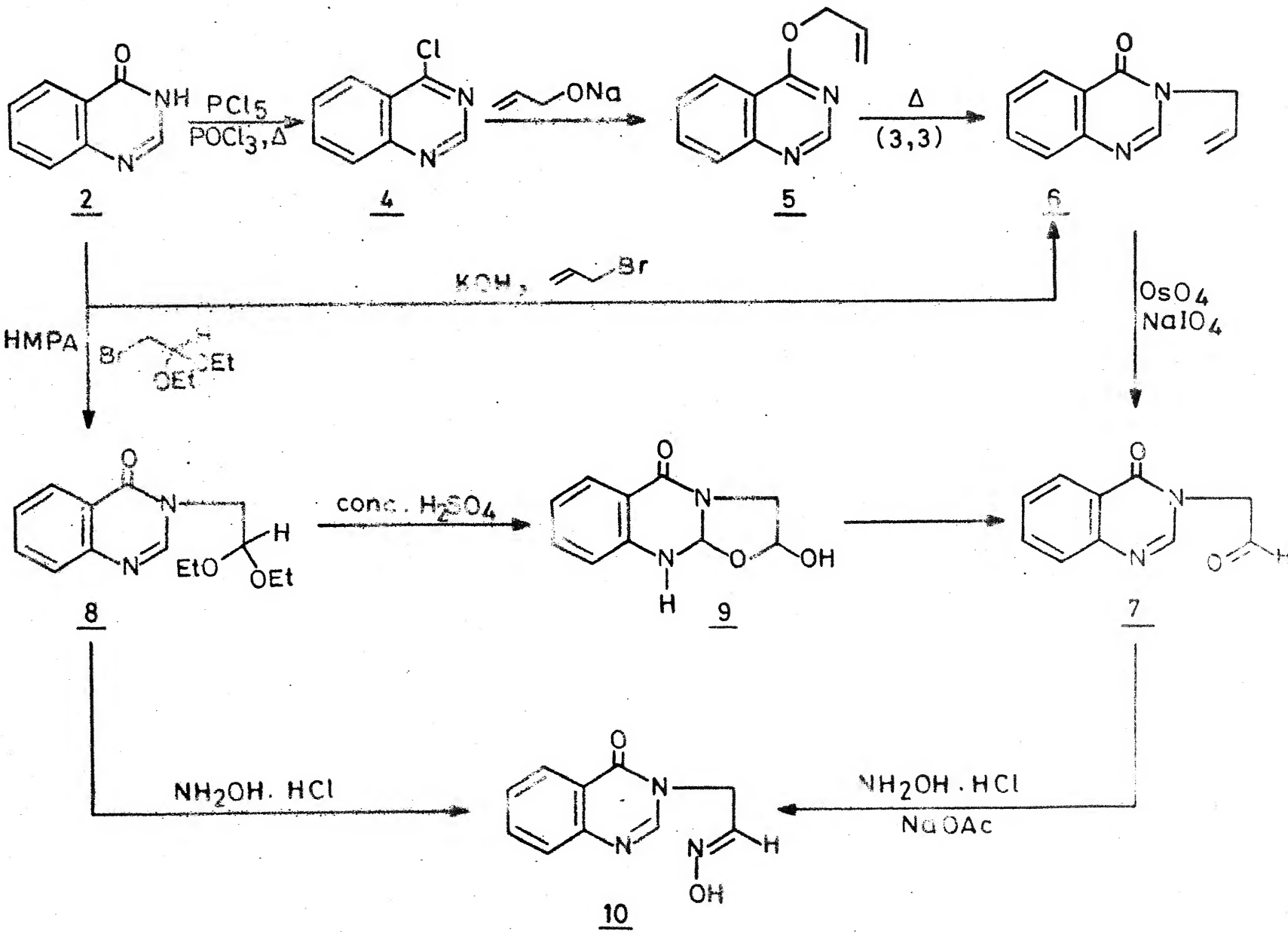
6 : mp. 65°C

ir : ν_{max}(KBr) cm^{-1}: 1675 (amide carbonyl), 1615, 1570 (C=C, C=N).

nmr: δ ($CDCl_3$) 60 MHz: 4.55 (dd, 2H, -N-$\underline{CH_2}$-CH-), 5.4(m, 2H, -CH=$\underline{CH_2}$), 6.1 (m, 1H, -$\underline{CH}$=CH_2), 7.25-8.5 (m, 4H, benzene ring), 8.66 (s, 1H, pyrimidine ring).

The formation of 6 by a [3,3] shift in 5 establishes the site of alkylation in the desired 3-position. Initially we felt that this was needed, not only to illustrate a strategy that would lead to the desired specific nitrogen alkylation, but also to ensure that the first stage relating to the chemical simulation, namely, the alkylation has taken place in the desired manner. It may be noted that in the case of 3,4-dihydro-4-oxoquinazoline(2) alkylation with an allyl residue could take place either at the 1 or the 3-positions. In the initial stages of the development of the chemistry of quinazolines, there had been some discussion about the site of alkylation. Currently, such alkylations derived from the conjugate base of 2 are assigned the 3-alkylated structures. In the present case having a specifically N^3-alkylated quinazoline, namely, 6, at hand, it was possible to correlate this product with that obtained by direct alkylation of the conjugate base 2 with allylbromide. The compounds obtained *via* both pathways were identical. A similar set of correlations were carried out by further transformation of the [3,3] product 6. Parenthetically, such correlations were considered to be important not only because of the need to ensure the site of alkylation but also to obtain

such compounds by direct procedures. The Osmium tetroxide-periodate cleavage of the specifically N^3-alkylated quinazoline 6 gave rise to the isolation of the aldehyde 7 as the unusual "hydrate" 9. The 9 → 7 interconversion was found to be extremely facile. Thus, whilst 9 showed in the ir spectrum, bands for hydroxyl and none for the aldehyde, on drying 9 over P_2O_5, it was readily transformed to the expected aldehyde 7 and possessing in the ir, the expected carbonyl functional group at 1730 cm^{-1}. The nmr spectrum of the OsO_4 - periodate cleaved product taken either in $CDCl_3$ or DMSO-d_6 showed that it was nearly completely the aldehyde 7, by virtue of the presence of the anticipated sharp signal at ~ 8.3, for the C^2-proton of the quinazoline system. Such an unusual behaviour was exhibited by the carbonyl group in the cases of the 6-nitro analog 16 and the 2-methyl analog[38]. Both these compounds exist normally as the cyclic system related to 9. Another interesting feature of this system is that attempted transformation of either 7 or 9 with NH_3 to the Schiff base gave rise to the tricyclic system 11 (vide infra). The unusual behaviour of the 2'-oxoethyl system attached to the 3-Nitrogen is best explained on the basis of structure 9. The alternate possibility, namely, that relating to hydrogen bonding with the 4-oxo group is unlikely, not only because it would call for a 7-membered hydrogen bonded system, but also this carbonyl function behaved normally in the ir. As anticipated, reaction of either 7 or 9 with hydroxylamine hydrochloride led to the isolation of oxime 10 in excellent yields without complication (CHART C.2).


PCl5
POCl3,Δ
ONa
Δ
(3,3)
2
4
5
6
KOH,
Br
HMPA
OsO4
NaIO4
conc. H2SO4
8
9
7
NH2OH. HCl
NH2OH . HCl
NaOAc
10

7 : mp. 152°C

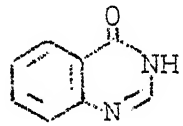
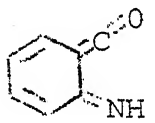
ir : ν_{max}(KBr) cm^{-1}: 1720 (aldehyde), 1675 (amide carbonyl).

nmr: δ(DMSO-d_6) 500 MHz: 6.15 (d, 2H, -N-C$\underline{H}_2$-CH), 7.52 (t, 1H, 6'-quinazoline ring), 7.66 (d, 1H, 8'-quinazoline ring), 7.8 (t, 1H, 7'-quinazoline ring), 8.15 (d, 1H, 5'-quinazoline ring), 8.22 (s, 1H, 2'-quinazoline ring).

9 : ir : ν_{max}(KBr) cm^{-1}: 3400 (br)(OH), 1710 (very weak) (aldehyde), 1675 (amide carbonyl).

10: mp. 163-4°C

Mass:m/e: 203(M^+), 186(M^+-OH), 159 (M^+-.HC=N-OH),

146 ()$^+$, 119 ()$^+$.

ir : ν_{max}(KBr) cm^{-1}: 1680 (amide carbonyl), 1615, 1515 (C=C, C=N).

nmr: δ(DMSO-d_6) 200 MHz: 4.75 (d,d, 2H, -N-C$\underline{H}_2$-), 6.88, 7.5 (t,t, 1H, -C$\underline{H}$=N-OH), 7.5 (m, 1H, 6'-quinazoline ring), 7.65 (d, 1H, 8'-quinazoline ring), 7.8 (t, 1H, 7'-quinazoline ring), 8.15 (d, 1H, 5'-quinazoline ring), 8.35 (d, 1H, 2'-quinazoline ring), 11.0,11.35 (s,s, 1H, =N-O$\underline{H}$).

Interestingly, the 7 → 9 change represents the cyclisation that is the second step relating to the chemical simulation of the ATP-Imidazole Cycle. Indeed, specific cleavage of this, leading to the detachment of the anthranilic acid unit would lead to oxazole. In the event however, endeavours to achieve this under a variety of conditions invariably gave the aldehyde, a consequence that was not unanticipated. A similar behaviour was exhibited by the 6-nitro analog 16 as well as 11.

Having a set of authentic, useful, funtionalised, N^3-alkylated compounds at hand, endeavours were made to delineate conditions under which these compounds could be prepared in a more expedious manner. In the event, the reaction of the sodium salt of 4-oxoquinazoline in HMPA, with the diethyl acetal of bromoacetaldehyde, gave the expected ketal in excellent yields. It was found that alkylations in other solvent systems did not proceed at all. The structural assignment for ketal 8 is based on spectral and analytical data (CHART C.2).

---

8 : mp. 79°C

ir : ν_{max}(KBr) cm^{-1}: 1680 (amide carbonyl), 1615, 1565 (C=C, C=N).

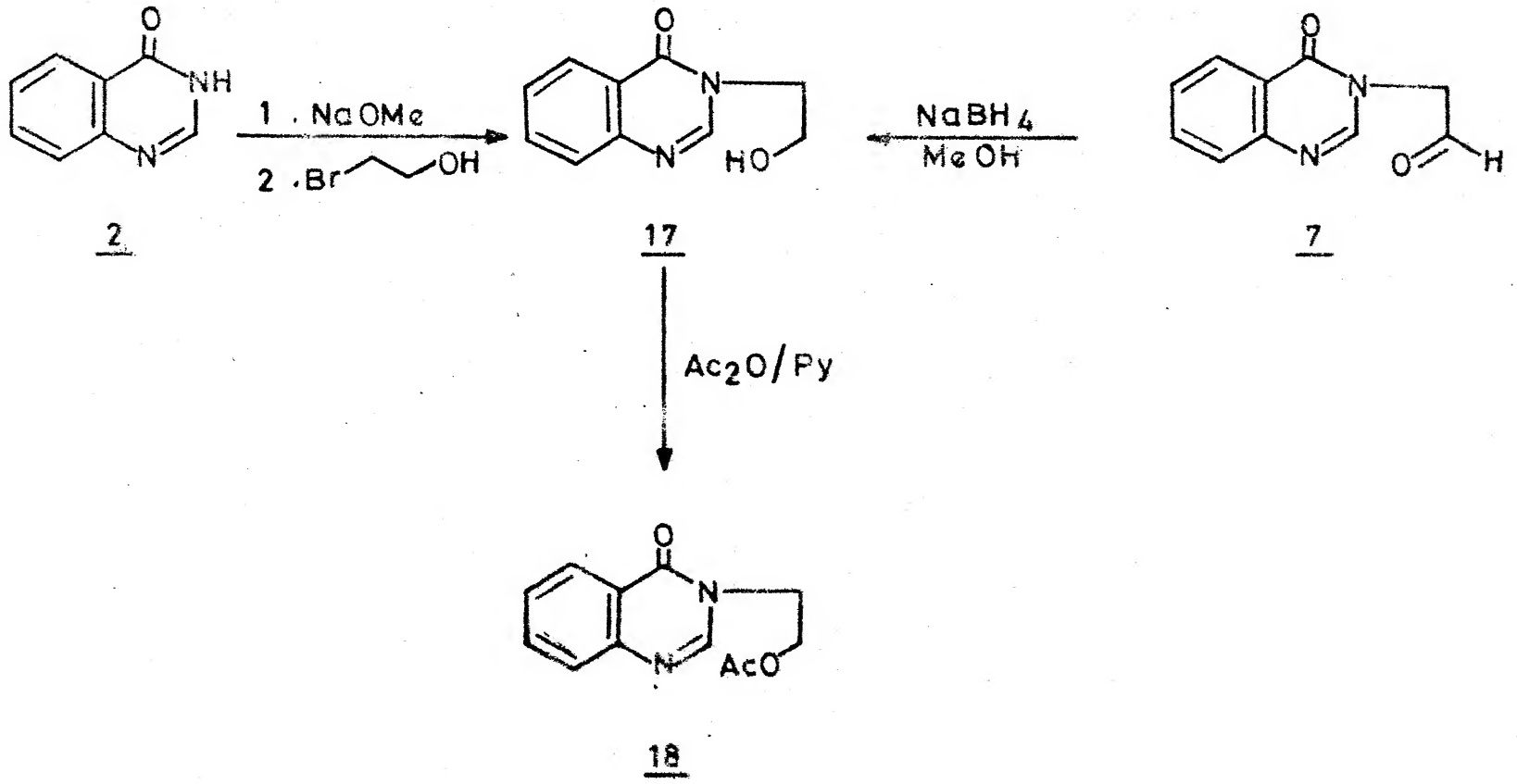
nmr: $\delta(CDCl_3)$90 MHz: 1.15 (t, 6H, $-CH_2-\underline{CH_3}$), 3.58 (m, 4H, $-\underline{CH_2}-CH_3$), 4.0 (d, 2H, $-\underline{CH_2}-CH-$), 4.65 (t, 1H, $-CH_2-\underline{CH}-$), 7.1-7.7 (m, 3H, 6',7',8'-quinazoline ring),

7.95 (s, 1H, 2'-quinazoline ring), 8.15 (d, 1H, 5'-quinazoline ring).

In the initial stages several attempts to hydrolyse the ketal 8 to either the aldehyde 7 or its hydrate 9 failed. Eventually, it was found that the desired change could be accomplished in 74.4% yields by brief warming of the ketal in conc. H_2SO_4, which led to 9, whose properties were identical to that obtained *via* degradation of the [3,3] shift product 6. In sharp contrast, the ketal 8 was transformed directly to the oxime 10 in good yields. The properties of 10 thus obtained were identical to that prepared *via* transformations on the [3,3] shift product 6.

The aldehyde 7 or its hydrate 9, underwent ready sodium borohydride reduction giving rise to the 2-Hydroxyethyl quinazolone 17 which was also prepared in a direct manner by alkylation of 2 *via* its conjugate base with 2-bromoethanol[39,40]. Compound 17 can also be used as an intermediate in the chemical simulation of the cycle, since such a series of reactions with 17 could be anticipated to lead to the daughter product oxazoline and the template anthranilic acid (CHART C.IV). The structural assignment for 17 is supported by spectral and analytical data and also by its transformation to the acetyl derivative 18 (CHART C.5).

CHART . C . 5



2 17 7

18

17: mp. 157°C

ir : ν_{max}(KBr) cm^{-1}: 3250 (OH), 1670 (amide carbonyl), 1610, 1560 (C=C, C=N).

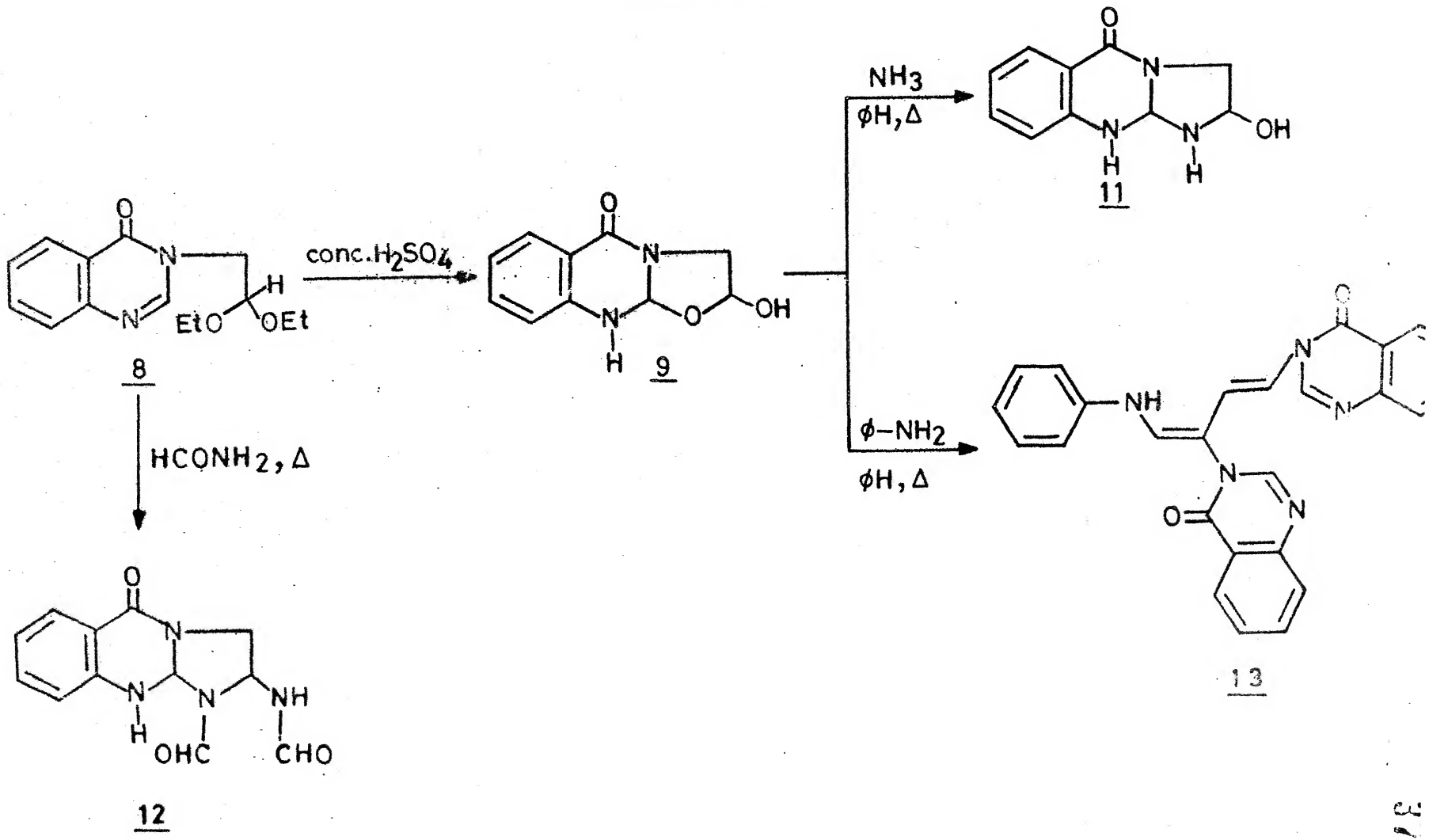
nmr: δ (DMSO-d_6) 500 MHz: 3.7 (2H, -N-C<u>H</u>$_2$-), 4.05 (2H, -C<u>H</u>$_2$-OH), 4.5-8.3 (5H, aromatic).

18: mp. 79°C

nmr: δ ($CDCl_3$) 60 MHz: 2.1 (s, 3H, -CO-C<u>H</u>$_3$), 4.4 (m, 4H, -C<u>H</u>$_2$-C<u>H</u>$_2$-O), 7.5-7.9 (m, 3H, 6',7',8'-quinazoline ring), 8.1 (s, 1H, 2'-quinazoline ring), 8.4 (d, 1H, 5'-quinazoline ring).

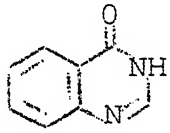
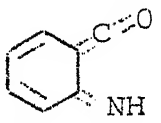
It was anticipated that either the aldehyde <u>7</u> or its hydrate <u>9</u> or even the diethylacetal <u>8</u> could be advantageously used in the placement of the appropriate terminal nitrogen, which on cyclisation and rupture, could lead to imidazole. It could be readily seen that the Schiff base arising from <u>7</u> would be an ideal precursor. Consequently, the hydrate <u>9</u> was treated with dry NH_3 in refluxing benzene, under conditions where water could be removed from the reaction mixture. Surprisingly, the sole product that was obtained was the tricyclic compound corresponding to the addition of elements of NH_3 to the aldehyde <u>7</u>. The structural assignment for <u>11</u> is supported by spectral and analytical data (CHART C.3).

CHART . C . 3



11: mp. 177°C

Mass:m/e: 188 (M^+-NH_3), 159 ($M^+-CH(OH)NH_2$),

146 ()$^+$, 119 ()$^+$.

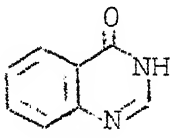
ir : ν_{max}(KBr) cm^{-1}: 3450 (OH), 3280, 3240 (NH), 1675 (amide carbonyl), 1610, 1565 (C=C, C=N).

nmr: δ(DMSO-d_6) 200 MHz: 3.85 (m, 3H, -C<u>H</u>$_2$-C<u>H</u>-), 7.45 (d, 1H, 6'-quinazoline ring), 7.5 (d, 1H, 8'-quinazoline ring), 7.7 (m, 1H, 7'-quinazoline ring), 8.05 (d,1H, 5'-quinazoline ring), 8.1 (s, 1H, 2'-quinazoline ring).

With the objective of transforming 7 to the N-phenyl Schiff base, the hydrate 9 was refluxed with aniline in benzene under conditions where water formed in the reaction was removed. Surprisingly, the sole product that could be isolated in this reaction was the dimeric product 13 (15%), whose structure is supported by spectral and analytical data (CHART C.3). The transformation of the aldehyde 7 → 13 could be readily rationalised via sequence, the formation of the anticipated Schiff base and its transformation to the enamine by prototropic shift. This enamine rather than undergoing intramolecular cyclisation that could lead to the template mediated synthesis of N-phenyl imidazole

reacted with another molecule of the aldehyde 7, which, on dehydration followed by prototropic shift, yielded the dimeric product 13.

13: mp. 235°C

Mass:m/e: 433 (M^+), 287 (M^+- ).

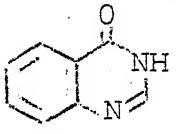
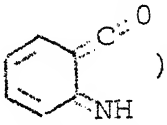
ir : ν_{max}(KBr) cm^{-1}: 3310(NH), 1690 (amide carbonyl), 1630, 1600, 1566 (C=C, C=N).

nmr: δ(DMSO-d_6) 500 MHz: 6.25, 6.3 (d,d, 1H, -CH=C<u>H</u>-Q), 8.48, 8.66 (s,s, 1H, -NH-C<u>H</u>=CH-), 6.75-8.25 (m,15H, aromatic), 8.66 (m, 1H, -CH=C-C<u>H</u>=CH-).

In another set of experiments, the ketal 8 was treated with formamide with the anticipation that an N-formyl Schiff base may result. In the event, the reaction gave rise to a bis formamide adduct for which the tricyclic structure 12 (36.6%) has been assigned on the basis of spectral and analytical data as well as the earlier described behaviour of 7 to form tricyclic systems. The formation of 12 could be rationalised on the basis of the formation of the N-formyl Schiff base which underwent intramolecular addition followed by acceptance of another unit of formamide, a sequence that is very similar to the formation of 9 from 7. It may be noted that compound 12 could be processed

through the cycle *via* cleavage leading to an imidazole or an imidazoline. In the event, however, as with the case of similar studies with 9, this objective could not be realised (CHART C.3).

12: mp. 254°C

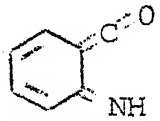
Mass: m/e: 260(M^+), 215 (M^+-H_2N-CHO), 160 (M^+-.$CH(CONH_2)_2$, 146  $)^+$, 119 ( $)^+$.

ir : ν_{max}(KBr) cm^{-1}: 3310 (NH), 1670 (br) (formyl, ring amides), 1610, 1540 (C=C, C=N).

Our studies on the mechanism of the nitroethylation of amines[41] enabled the discovery of a novel entry to specifically N^3-alkylated-4-oxoquinazolines. A condition that is necessary for the successful nitroethylation of amines is the opportunity for the self quenching of the initially formed zwitter ion. This condition is admirably realised in the case of 3,4-dihydro-4-oxoquinazoline which is known to exist in equilibrium with the tautomeric 4-hydroxyquinazoline[42]. The latter structural contribution enables the delivery of the required proton to the initially formed zwitter ionic product with nitroethylene. As predicted, compound 2 underwent smooth nitroethylation leading to 3-(2'-nitroethyl)-4-oxoquinazoline (19) in excellent yields. The

structural assignment for 19 is fully supported by spectral and analytical data (CHART C.6).

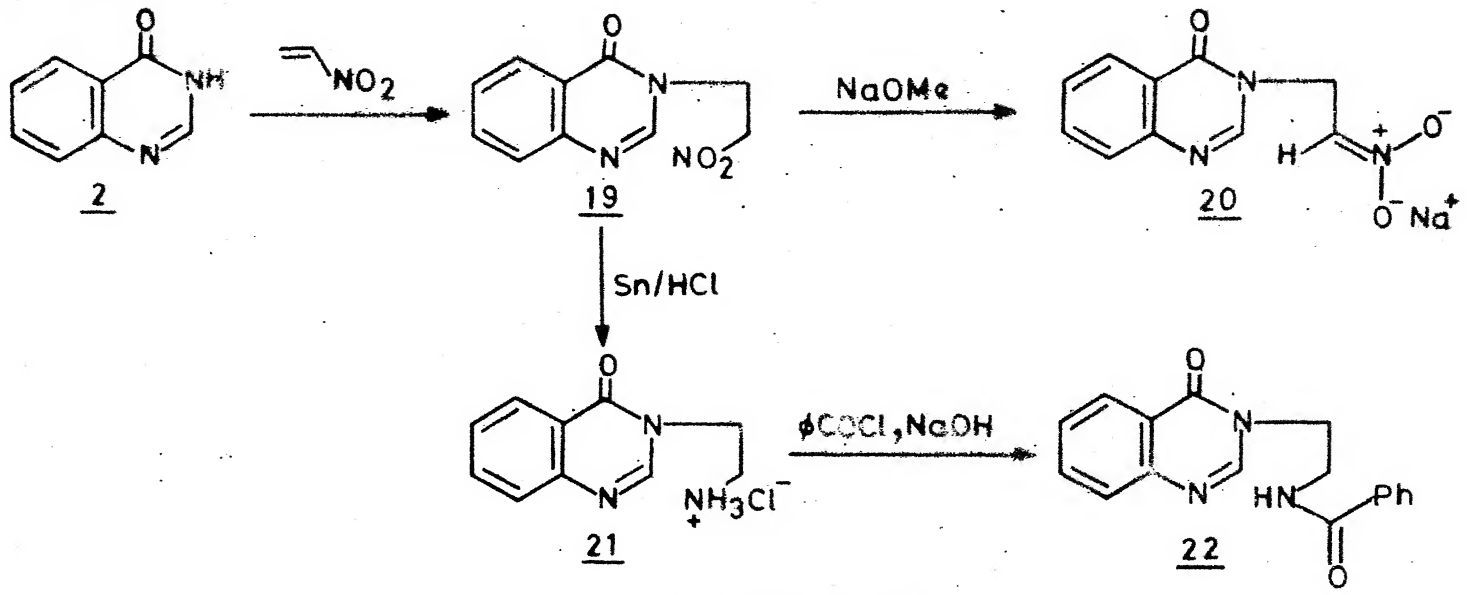
19: mp. 118-9°C

Mass: m/e: 219 (M^+), 173 (M^+-.NO_2), 159 (M^+-.CH_2-NO_2), 145 (M^+-.CH_2-CH_2-NO_2), 119 ()$^+$.

ir : ν_{max}(KBr) cm^{-1}: 1660 (amide carbonyl), 1615 (C=C), 1550, 1355 (NO_2).

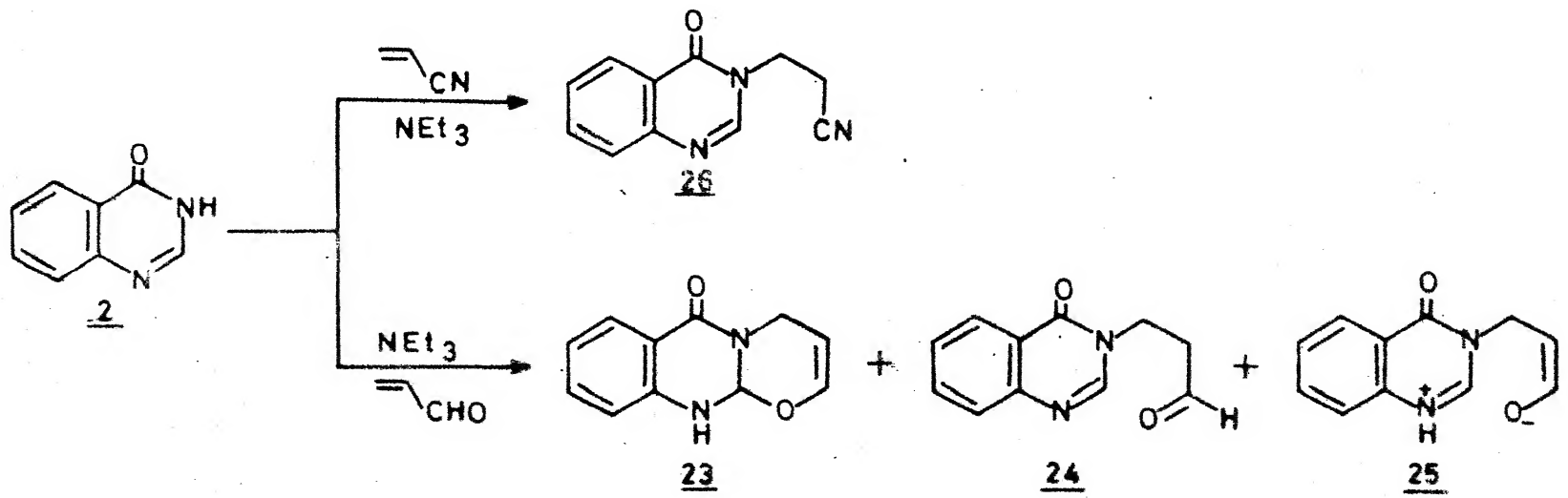
nmr: $\delta(CDCl_3)$ 500 MHz: 4.54 (t, 2H, -N-C<u>H</u>$_2$-), 4.88 (t, 2H, -C<u>H</u>$_2$-NO_2), 7.53, 7.78 (t,t, 1H, 1H, 6',7'-quinazoline ring), 7.72 (d, 1H, 8'-quinazoline ring), 8.1 (s, 1H, 2'-quinazoline ring), 8.28 (d, 1H, 5'-quinazoline ring).

The nitro group of the specifically N^3-alkylated compound 19 was then transformed to useful functionalities that could be placed in the cyclic operation, leading to the daughter molecule. With the objective to transform the nitroethyl compound 19 to the aldehyde 7 via the 'Nef' reaction, it was transformed to the nitronate salt with sodium methoxide in excellent yields. However, further reactions of 20 with acids led to the recovery of unchanged 19 and no aldehyde 7 could be isolated. It is known that substrates that could accept protons, other than the nitronate unit,



2 19 20 21 22

CHART . C.7



2 26 23 24 25

do not undergo 'Nef' reaction. Compound 19 could be reduced to the amine dihydro chloride[39] 21 and then benzoylated to 22. Both 21 and 22 would be useful precursors pertaining to the cycle (CHART C.6).

20: ir : ν_{max}(KBr) cm^{-1}: 3500 (br)(salt), (1530-NO_2 absent).

21: mp. 259-60°C (dec)

ir : ν_{max}(KBr) cm^{-1}: 3400-3200 (br) (NH salt), 1710 (amide carbonyl).

22: mp. 176-7°C

ir : ν_{max}(KBr) cm^{-1}: 3300 (NH), 1670 (amide carbonyl), 1625, 1530 (secondary amide).

nmr: $\delta(CDCl_3)$ 200 MHz: 3.74 (q. 2H, $-C\underline{H}_2-NH-$), 4.22 (t, 2H, $-N-C\underline{H}_2-$), 7.25-7.8 (m, 9H, $-N\underline{H}-CO-$, aromatic), 7.9 (s, 1H, 2'-quinazoline ring), 8.1 (d, 1H, 5'-quinazoline ring).

It may be recalled that 3-(2'-Hydroxy ethyl)-3,4-dihydro-4-oxoquinazoline (17) was prepared either *via* further transformations of the [3,3] shift product 6 or more directly by alkylation with 2-bromoethanol (CHART C.5). A similar alkylation of 2 with 1,2-dibromoethane gave in very good yields the 2'-bromoethyl

compound[43] 27 which was transformed readily, with aniline to the desired, appropriately functionalised, N^3-alkylated product 28 in 95% yields. The structural assignment for 27 and 28 is supported by spectral and analytical data (CHART C.8).

27: mp. 116°C

ir : ν_{max}(KBr) cm^{-1}: 1670 (amide carbonyl), 1620, 1610 1560 (C=C, C=N).

nmr: $\delta(CDCl_3)$ 60 MHz: 3.7 (t, 2H, -N-C<u>H</u>$_2$-), 4.35 (t, 2H, -C<u>H</u>$_2$-Br), 7.2-7.8 (m, 3H, 6',7',8'-quinazoline ring), 8.05 (s, 1H, 2'-quinazoline ring), 8.2 (m, 1H, 5'-quinazoline ring).

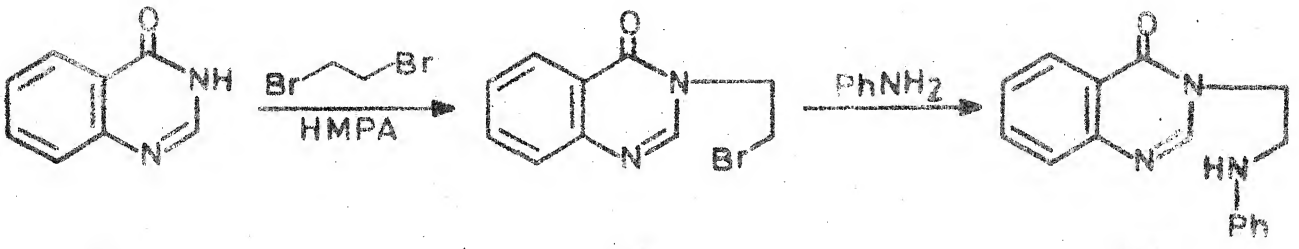
28: mp. 143-5°C

ir : ν_{max}(KBr) cm^{-1}: 3260 (NH), 1675 (amide carbonyl), 1600, 1560 (C=C, C=N).

nmr: $\delta(CDCl_3)$ 60 MHz: 3.5 (m, 2H, -C<u>H</u>$_2$-NH-Ph), 4.2 (m, 3H, -N-C<u>H</u>$_2$-CH$_2$-N<u>H</u>-), 6.4-6.78 (m, 8H, 6',7',8'-quinazoline ring, phenyl), 7.85 (s, 1H, 2'-quinazoline ring), 8.25 (m, 1H, 5'-quinazoline ring).

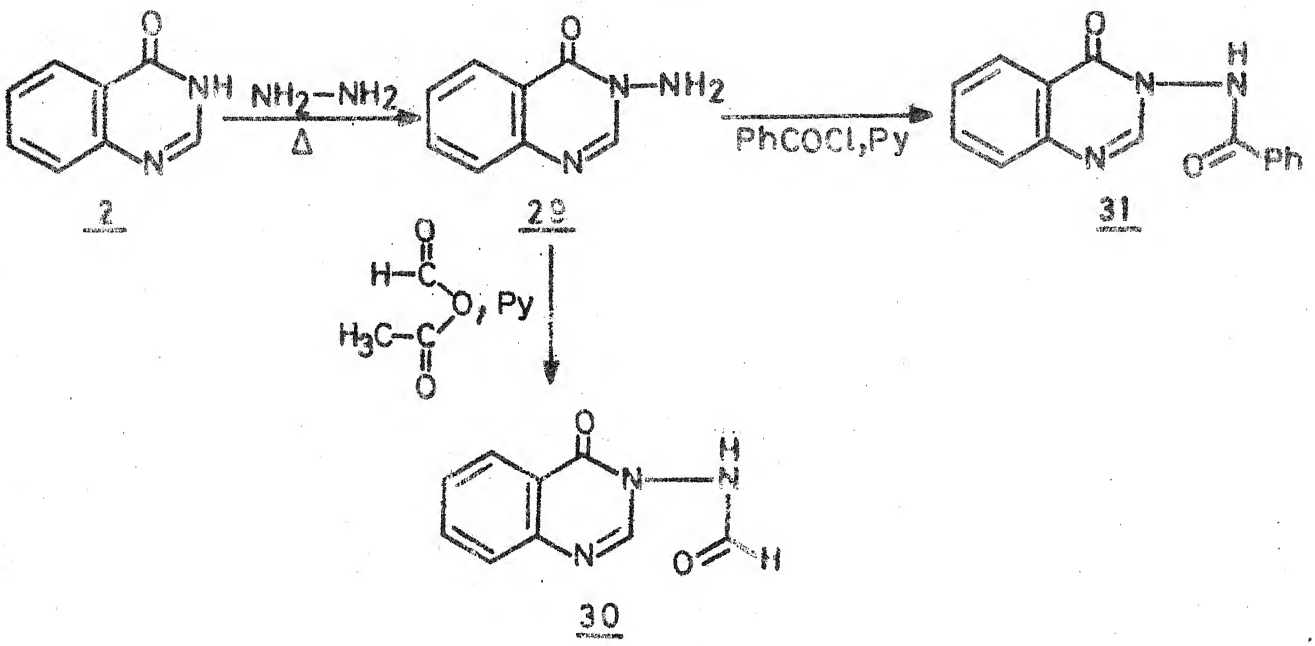
Michael addition of nitroethylene with the conjugate base of 2 could not be carried out because of the tendency of nitroethylene to undergo polymerisation under alkaline conditions.

CHART . C.8



2 27 28

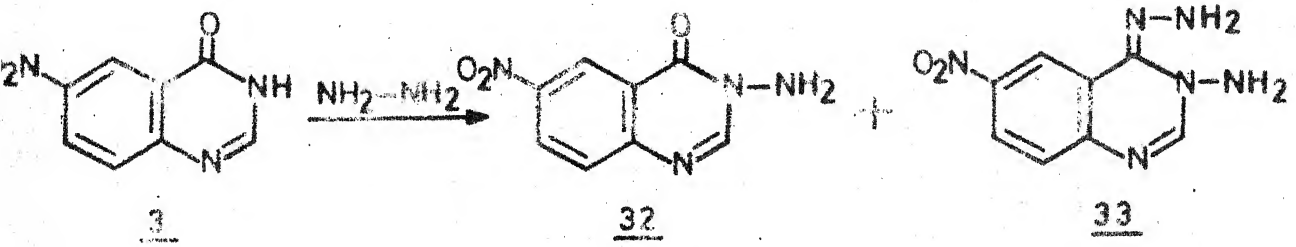
CHART C.9



2 29 31

30

CHART . C .10



3 32 33

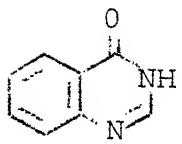
This problem does not arise in the case of very many acceptors, and in the present work, this aspect was demonstrated, by the Michael addition of the *in situ* generated conjugate base of 2 with acrylonitrile and acrolein. In the case of acrylonitrile the reaction was relatively smooth, leading to the formation of the expected adduct, namely, 3-(2'-cyanoethyl)-3,4-dihydro-4-oxoquinazoline (26) in 92% yields.[44] In sharp contrast, the reaction with acrolein gave rise to an equilibrating product composite, which is concluded to be, particularly on the basis of 200 MHz nmr, a mixture of the expected aldehyde 32, which, parenthetically, is the homologue of 7, and the tricyclic system 23, in the ratio 1:3. The nmr spectrum clearly showed a doublet at 3.3 ppm, which can be best explained on the basis of structure 23. The ready formation of such systems, exemplified with 9, 11 and 12 (*vide supra*), makes this conclusion quite reasonable (CHART C.7).

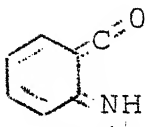
26: mp. 144-5°C

ir : ν_{max}(KBr) cm^{-1}: 2250 (C≡N), 1670 (amide carbonyl), 1610 (C=C).

nmr: δ($CDCl_3$) 60 MHz: 2.85 (t, 2H, $-CH_2-CN$), 4.2 (t, 2H, $-CH_2-CH_2-CN$), 7.5 (m, 3H, 6',7',8'-quinazoline ring), 8.25 (m, 1H, 5'-quinazoline ring).

23+25: mp. 79-81°C

Mass:m/e: 202 (M^+), 174 (M^+-CO), 146 ()$^+$,

119 ()$^+$.

ir: ν_{max}(KBr) cm^{-1}: 3120 (NH), 1670 (amide carbonyl), 1620, 1560 (C=C, C=N).

nmr: $\delta(CDCl_3)$ 60MHz : 3.1 (q, $-CH_2-CH=CH-$), 3.3 (d, ~70%, $-CH_2-CH=CH-$), 4.1 (q, ~70%, $-CH=CH-O$, 2'-quinazoline ring), 4.6 (br, ~70% NH), 9.7 (s, ~30%, -CHO), 7.5-8.2 (m, 5H, aromatic).

The work described thus far is related to the preparation of specifically N^3-alkylated, 3,4-dihydro-4-oxoquinazolines, that can be placed in a cyclic operation, leading to, the template molecule anthranilic acid on the one hand and a five membered heterocyclic system on the other, wherein the third position would be nitrogen and the first either an oxygen or a nitrogen atom. The synthesis of the N^3-substituted systems which can accommodate an additional nitrogen was also prepared in the present work using the key compound 3-amino-3,4-dihydro-4-oxo-quinazoline (29) which was prepared in excellent yields by the reaction of 2 with hydrazine hydrate[45]. Since 2 in turn was prepared from anthranilic acid, compound 29 is related to the basic template molecule in the series, namely anthranilic acid.

The 2 → 29 change involving an apparent substitution with an amino group, can be understood in terms of the nucleophilic addition of hydrazine to the 2-position of compound 2, cleavage generating an amide function and cyclisation with loss of NH_3[46,47]. (CHART C.9).

29: mp. 208°C

The N-amino compound 29 could be readily formylated with acetic formic anhydride[48] leading to 3-formamido-3,4-dihydro-4-oxoquinazoline (30), which when put through the cycle could lead to, as the daughter product, 1,3,4-oxadiazole, regenerating the parent template anthranilic acid. The structural assignment for 30 is supported by spectral data (CHART C.9).

30: mp. 152-3°C

ir : ν_{max}(KBr) cm^{-1}: 3420, 3180 (NH), 1710 (shoulder) (formyl), 1675 (ring amide), 1610, 1560 (C=C, C=N).

The N-amino compound 29 was also readily transformed to the benzoyl derivative[49] 31 which could be a precursor to 2-phenyl-1,3,4-oxadiazole (CHART C.9).

31: mp. 190-1°C

ir : ν_{max}(KBr) cm^{-1}: 3260 (NH), 1660 (amide carbonyl), 1610, 1510 (C=C, C=N).

In the first stage relating to the chemical simulation of the ATP-Imidazole Cycle, parellel synthetic studies were also carried out with the perturbed model template 5-nitro anthranilic acid and the template 5-aminoimidazole-4-carboxamide.

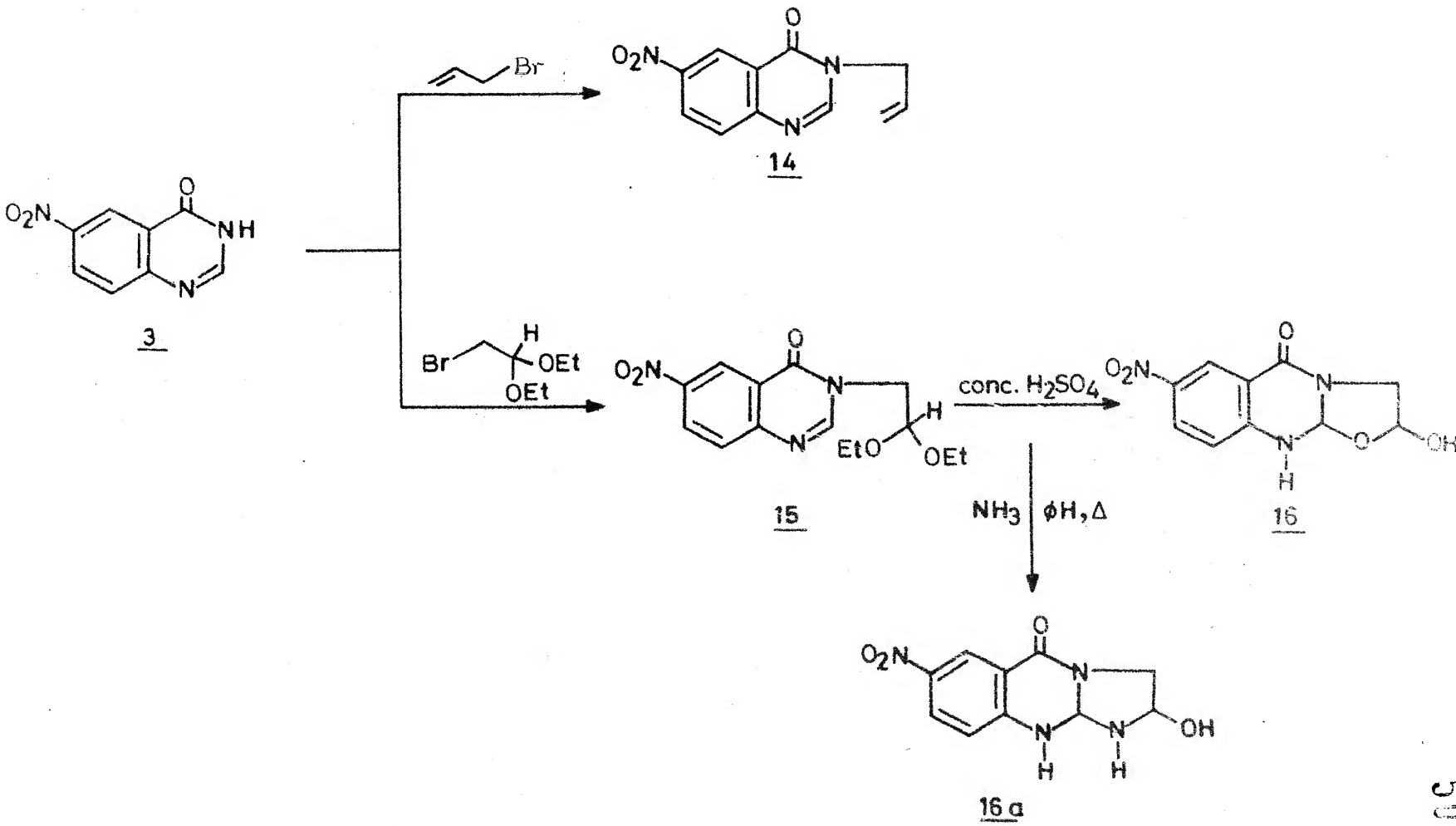
The reaction of 6-Nitro-3,4-dihydro-4-oxoquinazoline (3) derived from anthranilic acid (vide supra) was converted to the N^3-allyl compound 14 via alkylation of the conjugate base of 3 with allylbromide. The position of the ligand thus introduced is concluded to be at the 3-nitrogen, on the basis of studies on the unsubstituted precursors (CHART C.4).

14: mp. 148-50°C

ir : ν_{max}(KBr) cm^{-1}: 1675 (amide carbonyl), 1615, 1600, 1570 (C=C, C=N), 1520, 1350 (NO_2).

nmr: $\delta(CDCl_3)$ 200 MHz: 4.54 (d, 2H, -N-C<u>H</u>$_2$-), 5.2 (m, 2H, -CH=C<u>H</u>$_2$), 5.84 (m, 1H, -C<u>H</u>=CH$_2$), 7.66 (d, 1H, 8'-quinazoline ring), 8.08 (s, 1H, 2'-quinazoline ring),

CHART . C . 4



8.35 (dd, 1H, 7'-quinazoline ring), 8.85 (d, 1H, 5'-quinazoline ring).

The nitro compound 3 was readily alkylated with diethyl acetal of bromoacetaldehyde in HMPA, leading to the N^3-alkylated compound 15, which, in turn, was hydrolysed with warm conc. H_2SO_4 to the aldehyde 16, which as in the case of the unsubstituted aldehyde 7, predominantly exists as the hydrate (ir). Compound 16 or its hydrate on treatment with NH_3 under conditions where water formed in the reaction was removed, gave rise to the tricyclic adduct 16a corresponding to 11 (CHART C.4).

15: mp. 122-3°C

ir : ν_{max}(KBr) cm^{-1}: 1690 (amide carbonyl), 1615, 1600, 1570 (C=C, C=N), 1525, 1350 (NO_2).

nmr: $\delta(CDCl_3)$ 200 MHz: 1.2 (t, 6H, $-O-CH_2-C\underline{H}_3$), 3.6, 3.85 (m, m, 4H, $-O-C\underline{H}_2-CH_3$), 4.15 (d, 2H, $-N-C\underline{H}_2-$), 4.8 (t, 1H, $-N-CH_2-C\underline{H}-$), 7.9 (d, 1H, 8'-quinazoline ring), 8.6 (dd, 1H, 7'-quinazoline ring), 9.2 (d, 1H, 5'-quinazoline ring).

16: mp. 180-3°C

Mass:m/e: 233 (M^+), 205 (M^+-CO).

ir : ν_{max}(KBr) cm^{-1}: 1730 (aldehyde), 1690 (amide carbonyl), 1615, 1605 (C=C, C=N), 1525, 1345 (NO_2).

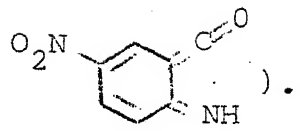
nmr: $\delta(CDCl_3)$ 200 MHz: 5.0 (s, 2H, $-C\underline{H}_2-CHO$), 7.95 (d, 1H, 8'-quinazoline ring), 8.08 (s, 1H, 2'-quinazoline ring), 8.65 (dd, 1H, 7'-quinazoline ring), 9.2 (d, 1H, 5'-quinazoline ring), 9.85 (s, 1H, $-C\underline{H}O$).

16a: mp. 220°C (dec)

ir : ν_{max}(KBr) cm^{-1}: 3500 (br)(OH), 3290 (NH_2), 1680 (amide carbonyl), 1610, 1570 (C=C, C=N), 1340, 1520 (NO_2).

Surprisingly, the reaction of the nitro compound 15 with hydrazine hydrate under conditions employed for the 2 → 29 change, gave, in addition to the expected N-amino compound 32 (29%), the hydrazone 33 (5.8%). The structural assignment for 32 and 33 is supported by spectral and analytical data. The formation of 33 could be rationalised on the further reaction of 32 with hydrazine. The presence of the nitro group withdraws the lone pair contribution away from the carbonyl, thus making it more electrophilic compared to 29 (CHART C.10).

32: mp. 220-2°C

Mass:m/e: 191 (M^+-.NH), 165 ().

ir : ν_{max}(KBr) cm^{-1}: 3500, 3380 (NH_2), 1660 (amide carbonyl), 1635, 1610, 1590 (C=C, C=N), 1300, 1490 (NO_2).

nmr: δ(DMSO-d_6)100 MHz: 4.6 (br, 2H, -N<u>H</u>$_2$), 6.6 (d, 1H, 8'-quinazoline ring), 7.6 (s, 1H, 2'-quinazoline ring), 8.0 (dd, 1H, 7'-quinazoline ring), 8.4 (d, 1H, 5'-quinazoline ring).

33: mp. 270°C (dec)

ir : ν_{max}(KBr) cm^{-1}: 3460, 3420, 3340, 3300 (NH_2), 1670 (C=N-N), 1350, 1530 (NO_2).

nmr: δ(DMSO-d_6)100 MHz: 5.7 (s, 2H, =N-N<u>H</u>$_2$), 5.9 (s, 2H, -N-N<u>H</u>$_2$), 7.2 (d, 1H, 8'-quinazoline ring), 7.4 (s, 1H, 2'-quinazoline ring), 7.6 (d, 1H, 7'-quinazoline ring), 8.1 (s, 1H, 5'-quinazoline ring).

<u>Synthesis of specifically N^1-alkylated purines</u>:

It may be noted that the key compound that was used in diverse transformations pertaining to the model template anthranilic acid was 3,4-dihydro-4-oxoquinazoline. Naturally, the intermediates that could be placed on the real ATP-Imidazole Cycle

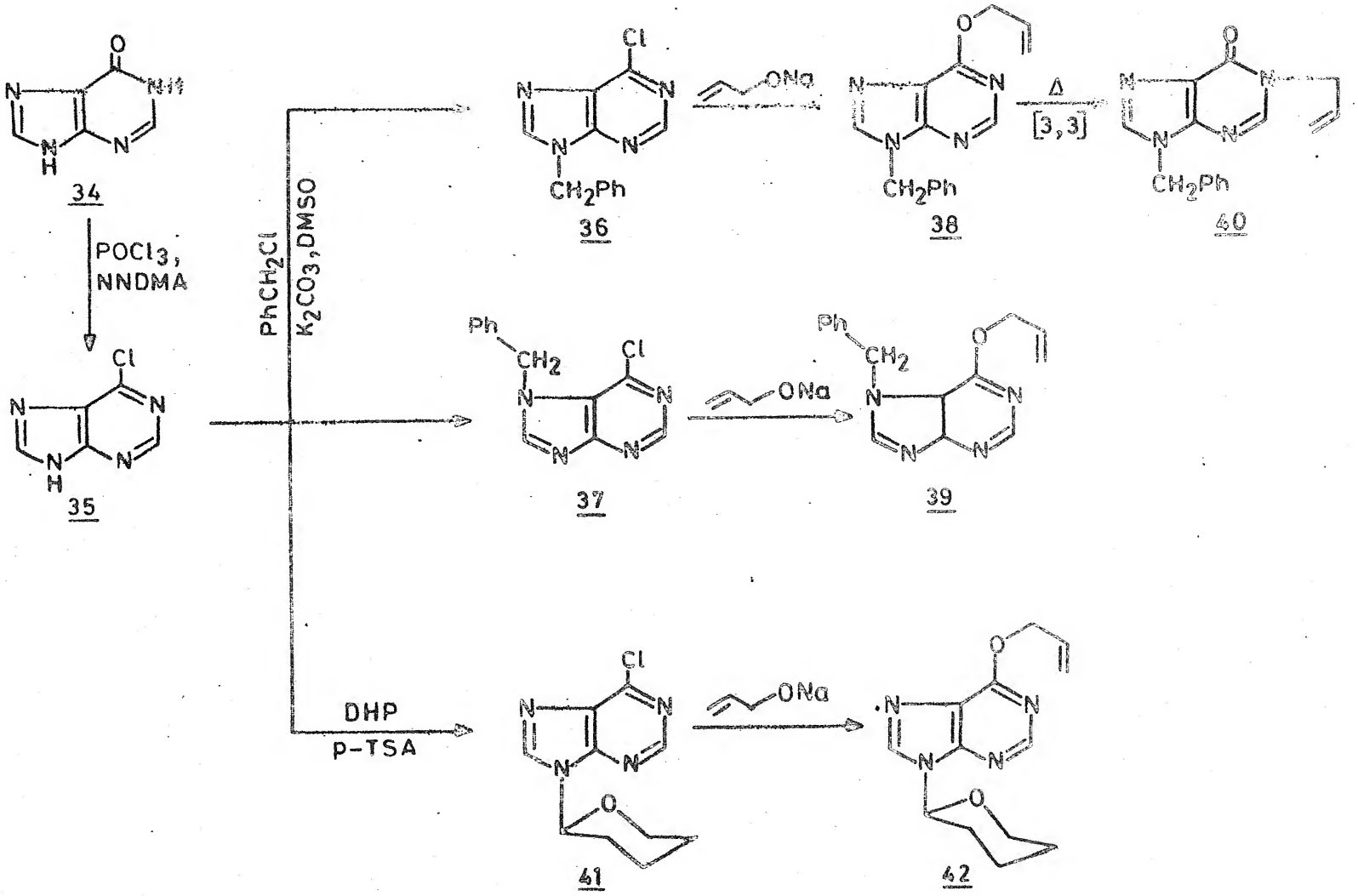
would be the closely related purines, hypoxanthine (34) and adenine (68), which can be, as is the case with 2, obtained readily from the imidazole template molecule 5-aminoimidazole-4-carboxamide[50]. However, in view of the presence of other reactive nitrogens in purines in contrast to 2, the imidazole ring nitrogens have to be protected[51-53]. In the initial stages of the present work, this was accomplished via the transformation of hypoxanthine (34) to 6-chloropurine (35) by reaction with $POCl_3$ and N,N-dimethylaniline[52,53]. Reaction of 35 with benzyl chloride, as reported[54] gave an easily separable mixture consisting of the desired 9-benzyl-6-chloropurine (36) (45%) and the isomeric 7-benzyl-6-chloropurine (37) (21%). It has been demonstrated that 6-chloropurine (35) can be specifically protected at the desired 9-position by dihydropyran[55], leading to 9-tetrahydropyranyl-6-chloropurine (41) which, interestingly, is quite similar to purines in which the 9-position is protected by sugar as in the ATP-Imidazole Cycle (CHART C.11). The structural assignment for 36, 37 and 41 is based on spectral data.

35: mp. > 360°C

36: mp. 89°C

ir : ν_{max}(KBr) cm^{-1}: 3100, 3050 (aromatic CH), 1600, 1560, 1540 (C=C, C=N).

CHART - C - 11


34
POCl3, NNDMA
35
PhCH2Cl
K2CO3, DMSO
DHP
p-TSA
36
37
41
ONa
38
39
42
Δ
[3,3]
40
CH2Ph
Ph
Cl

nmr: δ ($CDCl_3$) 60 MHz: 5.45 (s, 2H, $-C\underline{H}_2-\emptyset$), 7.3 (s, 5H, phenyl), 8.1 (s, 1H, imidazole ring), 8.7 (s, 1H, pyrimidine ring).

37: mp. 152°C

ir : ν_{max} (KBr) cm^{-1}: 3100, 3075 (aromatic CH), 1600, 1540, 1525 (C=C, C=N).

nmr: δ ($CDCl_3$) 60 MHz: 5.7 (s, 2H, $-C\underline{H}_2-\emptyset$), 7.3 (m, 5H, phenyl), 8.3 (s, 1H, imidazole ring), 8.8 (s, 1H, pyrimidine ring).

41: mp. 69°C

ir : ν_{max} (KBr) cm^{-1}: 3110 (aromatic CH), 2940, 2880 (saturated CH), 1595, 1565 (C=C, C=N).

Each of the protected derivatives 36, 37 and 41 on treatment with the conjugate base of allylalcohol gave rise to the anticipated O-allyl ethers 38, 39 and 42 in good yields (CHART C.11). The structural assignment for 38, 39 and 42 are supported by spectral and analytical data.

38: mp. 65°C

ir : ν_{max} (KBr) cm^{-1}: 3080, 3020 (aromatic, olefinic CH), 1600, 1580 (C=C, C=N), 1050 (C-O).

nmr: $\delta(CDCl_3)$ 60 MHz: 5.1 (m, 2H, -O-C<u>H</u>$_2$-), 5.38 (m, 4H, -C<u>H</u>$_2$-Ø), 6.18 (m, 1H, -C<u>H</u>=CH$_2$), 7.28 (s, 5H, phenyl) 7.8 (s, 1H, imidazole ring), 8.5 (s, 1H, pyrimidine ring).

<u>39</u>: mp. 84°C

ir : ν_{max}(KBr) cm^{-1}: 3110, 3060 (aromatic and olefinic CH) 1620, 1590, 1550 (C=C, C=N), 1070 (C-O).

nmr: $\delta(CDCl_3)$ 60 MHz: 5.0 (dd, 2H, -O-C<u>H</u>$_2$-), 5.3 (m, 2H, -CH=C<u>H</u>$_2$), 5.5 (s, 2H, -C<u>H</u>$_2$-Ph), 5.9 (m, 1H, -C<u>H</u>=CH$_2$), 7.1 (s, 5H, phenyl), 8.0 (s, 1H, imidazole ring), 8.5 (s, 1H, purine ring).

<u>42</u>: bp. 180-90°C/0.15 mm

ir : ν_{max}(neat) cm^{-1}: 3060 (aromatic, olefinic CH), 2940, 2850 (saturated CH), 1590, 1555 (C=C, C=N), 1040, 1050 (C-O).

nmr: $\delta(CDCl_3)$ 60 MHz: 1.9 (m, 6H, THP), 3.9 (m, 2H, -O-C<u>H</u>$_2$-THP ring), 5.0 (dd, 2H, -O-C<u>H</u>$_2$-CH-THP ring), 5.1-6.35 (m, 4H, -C<u>H</u>=C<u>H</u>$_2$, O-C<u>H</u>-THP ring), 7.9 (s, 1H, imidazole ring), 8.5 (s, 1H, pyrimidine ring).

Thermolysis of 9-benzyl-6-O-allylpurine <u>38</u> led to a smooth [3,3] shift giving rise to the specifically N^1-alkylated compound <u>40</u>. Parenthetically, to the best of our knowledge this is the

first demonstration of a [3,3] shift (Claisen rearrangement) on a 9-benzyl protected simple purine model[56].

40: mp. 114-5°C

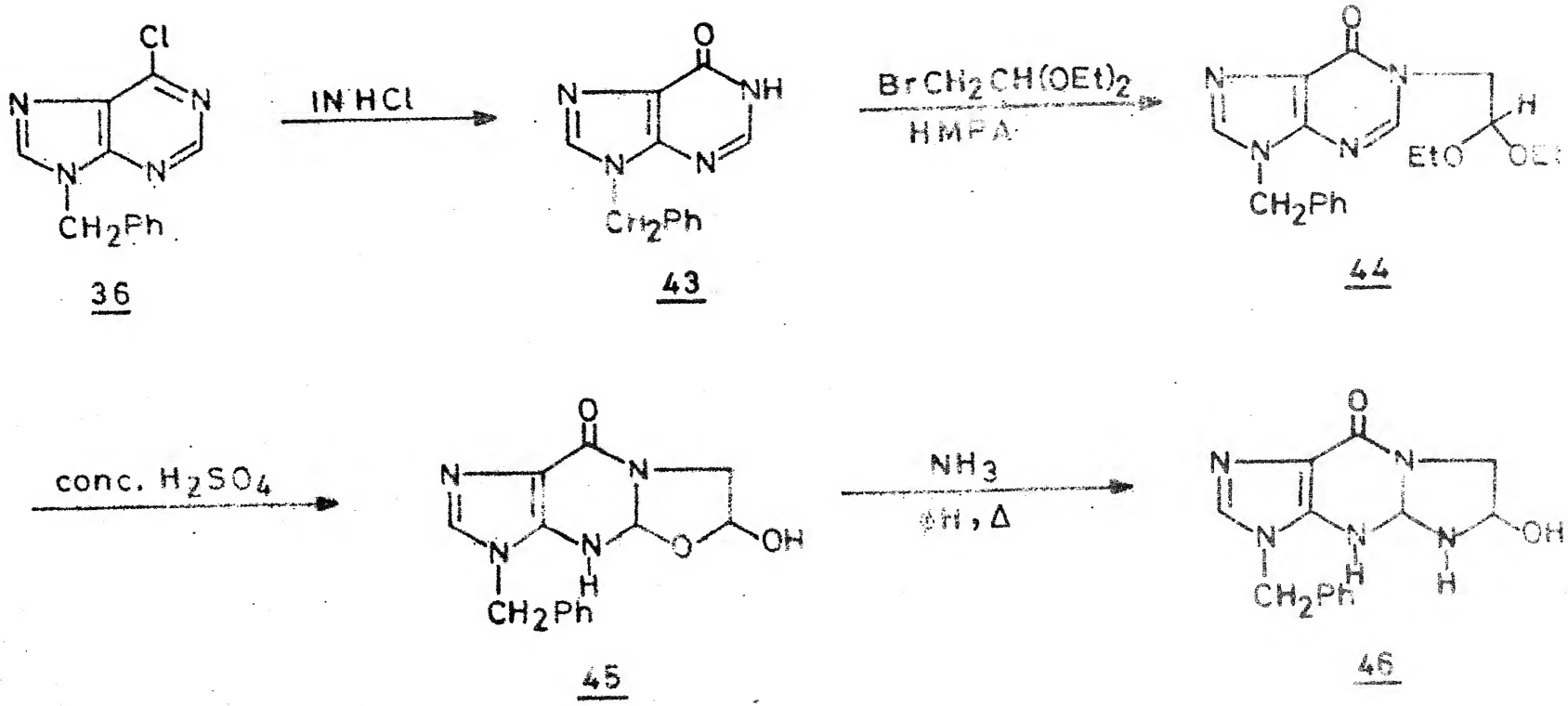
ir : ν_{max}(KBr) cm^{-1}: 3100, 3040 (aromatic and olefinic CH), 1685 (amide carbonyl), 1580, 1545, 1515 (C=C, C=N).

nmr: $\delta(CDCl_3)$ 60 MHz: 4.6 (dd, 2H, -N-C<u>H</u>$_2$-), 5.2 (m, 4H, -C<u>H</u>$_2$-Ø, -CH=C<u>H</u>$_2$), 5.9 (m, 1H, -C<u>H</u>=CH$_2$), 7.2 (s, 5H, phenyl), 7.6 (s, 1H, imidazole ring), 7.9 (s, 1H, pyrimidine ring).

The corresponding [3,3] rearrangement of the 7-benzyl compound 37 was found to be exceedingly slow and the 9-tetrahydropyranyl-6-O-allyl compound 42 fragmented to a mixture of compounds under conditions for the [3,3] rearrangement.

The specific N^1-alkylation of purines was achieved with 9-benzyl hypoxanthine (43), which was prepared from 6-chloro 9-benzylpurine (36), by hydrolysis, under conditions developed as a result of a great deal of experimentation with 1N HCl[57,58] (CHART C.12). Compound 43 was alkylated with the diethyl acetal of bromoacetaldehyde in HMPA under conditions developed for the 2 → 8 change, leading to the specifically N^1-alkylated 9-benzylhypoxanthine 44. Compound 44 was, in turn, transformed to the

CHART - C .12



36 43 44

45 46

aldehyde 45, which as in the case of the model system 7, existed largely as the hydrate. Indeed, reaction of the aldehyde 45 or the "hydrate" with dry NH_3 in benzene led to the tricyclic system 46, quite analogous to 11. The structural assignments for compounds 43, 44, 45 and 46 are supported by spectral and analytical data. It could be readily seen that either compound 45 or its hydrate or the ammonia adduct 46 could readily be placed in the cycle for further transformations to the respective product molecules oxazole and imidazole regenerating the parent template N-benzyl-5-aminoimidazole-4-carboxamide. In the event, however, as was the case with the model series, the ready transformation of the resulting tricyclic systems to the parent aldehyde 45 under a variety of conditions precluded its being a suitable candidate for placement in the cycle (CHART C.12).

43: mp. 293°C

ir : ν_{max}(KBr) cm^{-1}: 1700 (amide carbonyl), 1590, 1550, 1520 (C=C, C=N).

44: mp. 119-20°C

ir : ν_{max}(KBr) cm^{-1}: 1685 (amide carbonyl), 1570, 1505 (C=C, C=N).

nmr: δ($CDCl_3$) 200 MHz: 1.08 (t, 6H, -O-CH_2-CH_3), 3.46, 3.7 (m,m, 2H, 2H, -O-CH_2-CH_3), 4.1 (d, 2H,-N-CH_2-CH-), 4.68 (t, 1H, -N-CH_2-CH-), 5.28 (s, 2H, -CH_2-Ø), 7.26 (m, 5H, phenyl), 7.7 (s, 1H, imidazole ring), 7.98 (s, 1H, pyrimidine ring).

45: mp. 130°C

Mass:m/e: 269 $(M + 1)^+$, 268 (M^+), 240 (M^+-CO), 149 $(M^+-CO-.CH_2-Ø)$, 91 $(CH_2-C_6H_5)^+$.

ir : ν_{max}(KBr) cm^{-1}: 1670 (br) (aldehyde, amide carbonyl), 1570, 1550, 1515 (C=C, C=N).

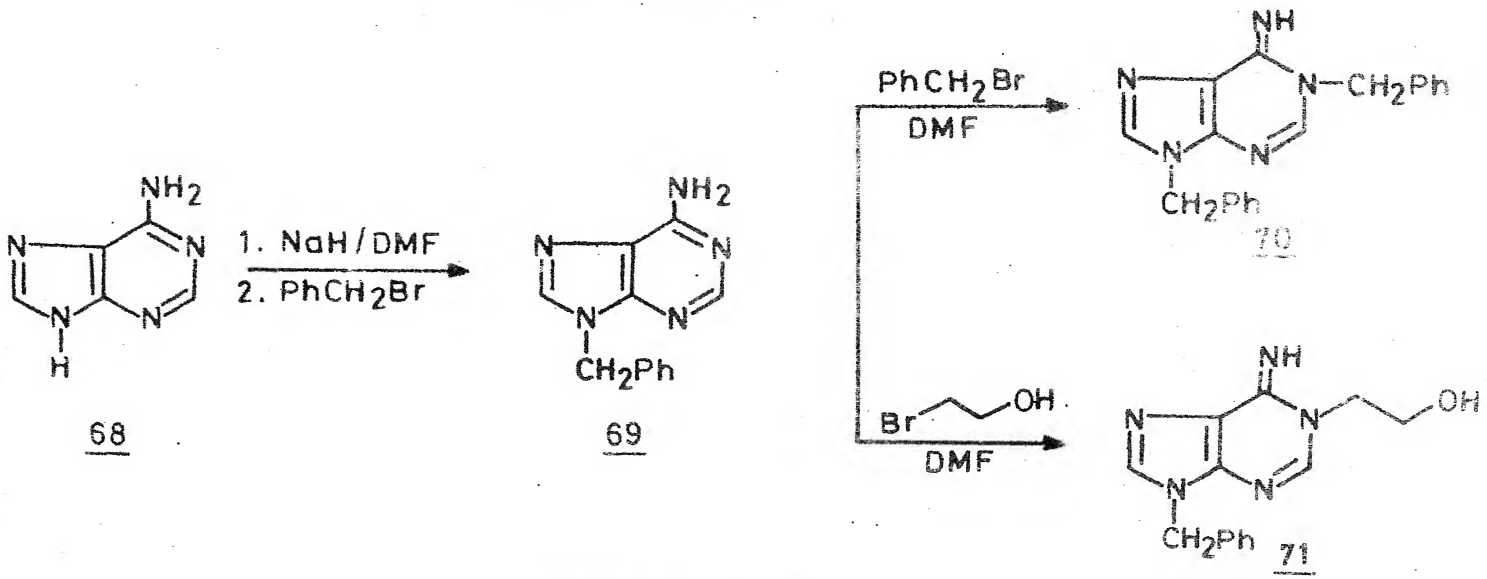
46: mp. 170°C (dec)

ir : ν_{max}(KBr) cm^{-1}: 3500-3300 (br) (OH), 3300, 3100 (NH), 1675 (amide carbonyl).

The reaction of 9-benzylhypoxanthine 43, with benzylbromide in DMSO gave smoothly the 1,9-dibenzylhypoxanthine (72)[59,60]. This reaction could be of importance,in the sense that such alkylations carried out with suitably substituted aryl halides could lead to the benzo analogs of monomeric heterocycles described earlier and the regeneration of the template molecule (CHART C.26).

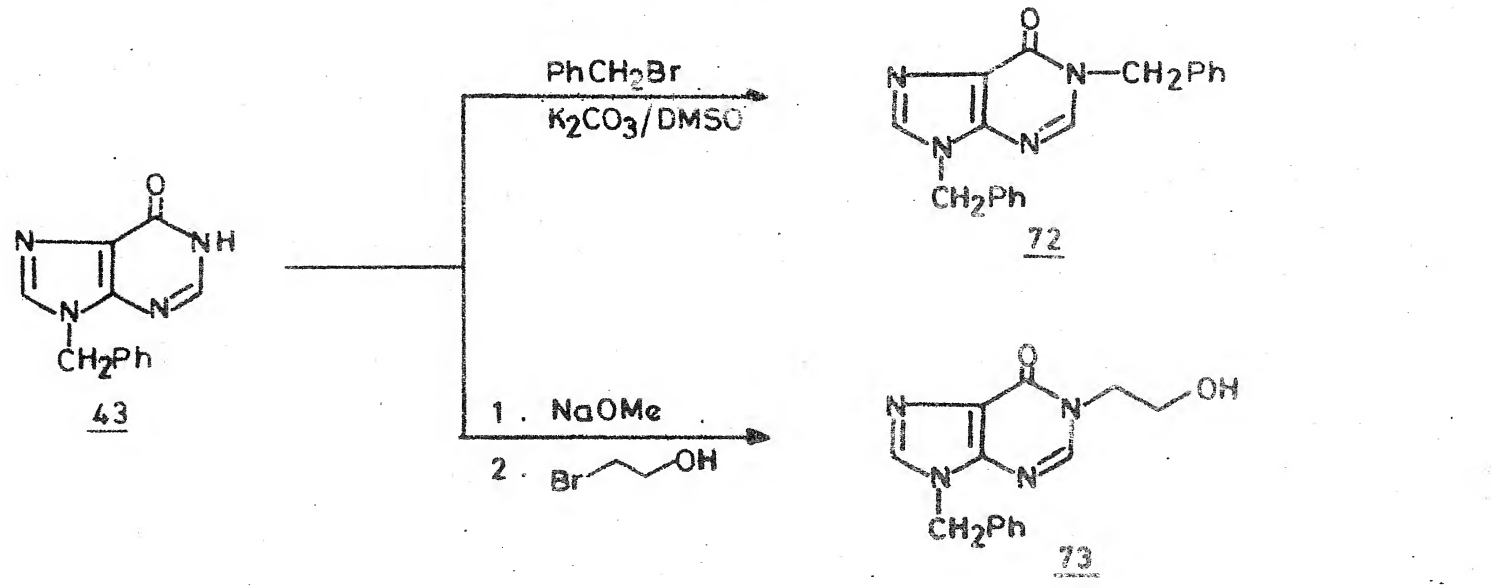
72: mp. 205°C

CHART . C . 25



68 69 70 71

CHART . C . 26



43 72 73

In a similar manner, the useful compound 1-(2'-hydroxy ethyl)-9-benzylhypoxanthine (73) was prepared from 9-benzyl-hypoxanthine by alkylation with 2-bromoethanol (CHART C.26).

73: mp. 172°C

ir : ν_{max}(KBr) cm^{-1}: 3400 (br)(OH), 1700 (amide carbonyl), 1600, 1570, 1550 (C=C, C=N).

Quite interesting results were obtained starting with adenine (68), which can be readily prepared from the template molecule 5-aminoimidazole-4-carboxamide. Compound 68 could be regiospecifically mono alkylated with NaH in DMF and benzyl-bromide[61] giving rise to 9-benzyladenine (69) in excellent yields. Of particular interest with reference to the ATP-Imidazole Cycle was the observation that 69 can be regioselectively alkylated at the 1-position giving rise to the neutral 1-(2'-hydroxy ethyl) imino compound 71. It may be recalled that in one of the later stages related to the chemical simulation of the ATP-Imidazole Cycle, the 4-carboxamide functionality of the template molecule is regenerated *via* hydrolytic cleavage of the 1-6 bond of a specifically N^1-alkylated adenine precursor. Indeed, at the outset, it was envisaged that the alkylation of 9-benzyladenine with 2-bromoethanol could lead to the corresponding salt, with a

charge on the, N^1-position and the retention of the 6-amino group, a situation that is very closely related to the ATP-Imidazole Cycle and one particularly favourable for the hydrolytic rupture of the 1-6 bond generating the amide function. However, the finding that such an alkylation actually resulted in the formation of the neutral imine 71 required an alternate strategy for the rupture of the 1-6 bond. This is contemplated in future work to be achieved by a fragmentation reaction on such an N-alkylated compound which, in addition, carry a suitable leaving group at the 1'-position. Such a substance could lead to the formation of 4-cyanoimidazole by fragmentation. Since the cyano group is a suitable precursor to the carboxamide moiety, such a strategy would be appropriate with reference to the chemical simulation of the cycle. It was considered possible that the desired N^1-alkylated adeninium salt could be prepared by altering the reaction conditions. To this effect the further alkylation of 9-benzyladenine was carried out with benzylbromide under a variety of conditions. It, however, turned out that in all cases the alkylation resulted in the formation of the neutral molecule 70. Parenthetically, this would serve as an excellent model for the study of the fragmentation strategy outlined earlier (CHART C.25). The structural assignment for 69, 71 and 70 are supported by spectral data.

69: mp. 234-5°C

nmr: δ(DMSO-d_6) 100 MHz: 5.4 (s, 2H, -C$\underline{H}_2$-Ø), 7.3 (m, 5H, phenyl), 8.0 (s,s, 1H, 1H, 2',8'-purine ring).

71: mp. 252°C

Mass:m/e: 251 (M^+-H_2O)

ir : ν_{max}(KBr) cm^{-1}: 3400 (br)(OH), 3340 (NH), 1680(C=NH).

nmr: δ(DMSO-d_6) 500 MHz: 3.75 (br, 2H, -N-C$\underline{H}_2$-), 4.45 (2H, -O-C$\underline{H}_2$-), 5.55 (s, 2H, -C$\underline{H}_2$-Ø), 7.4 (s, 5H, phenyl), 8.6, 8.7 (s,s, 1H, 1H, purine ring).

70: mp. 155-65°C

Mass:m/e: 315 (M^+), 224 (M^+-C_6H_5-CH_2.), 197 (M^+-C_6H_5-CH_2.-HCN), 106 (M^+-2$C_6H_5CH_2$.-HCN).

ir : ν_{max}(KBr) cm^{-1}: 3400 (br)(NH), 1670 (C=NH), 1620, 1575, 1520 (C=C, C=N).

nmr: δ(DMSO-d_6) 200 HMz: 2.25 (s, 1H, C=N$\underline{H}$), 5.45 (d, 4H, -C$\underline{H}_2$-Øx2), 7.3 (m, 10H, phenyl x 2), 8.45, 8.65 (s,s, 1H, 1H, 2',8'-purine ring).

Studies on the further transformations of specifically N-substituted quinazolines and purines, along the cycle, to daughter products and parent templates:

In the work that was outlined above, a variety of appropriately N-substituted compounds have been made, which could be

processed through, giving rise to the template on the one hand and the daughter product on the other. The protocol pertaining to the realisation of the further objectives are flexible in the sense that the sequences of reactions that are necessary, namely, the cyclisation and the detachment of the parent from the daughter can be sequentially arranged at will. In this context the several compounds that have been prepared could be categorised as those which are suitable for cyclisation first and cleavage subsequently, and those where the cleavage has to precede cyclisation. The criteria pertaining to this is on the basis of the correlation between the pKa of the side chain and that of the resulting cyclic system, since it was envisaged that the cyclisation of specifically N^3-substituted quinazolones can be best brought about <u>via</u> conjugate bases of the side chain ligands. Thus, as expected, those cyclisations that would lead to a considerably weaker conjugate base would be favoured. In contrast, where the pKa difference between the product and the starting material is marginal, other factors pertaining to the formation of the tricyclic system will influence the course of the reaction. Finally, those reactions where the product pKa would be higher than that of the starting material, can be considered as reactions that are unlikely to take place. In TABLE C.I are presented the estimated pKa values pertaining to the side chain of the N^3-substituted 3,4-dihydro-4-oxoquinazolines.

TABLE C.I

Estimated pKa values of N^3-substituted 3,4-dihydro-4-oxo-quinazolines

No.	Substitutent	Estimated pKa
6	$-C\underline{H}_2-CH=CH_2$	25
28	$-CH_2-CH_2-N\underline{H}-Ph$	25
26	$-CH_2-C\underline{H}_2-CN$	25
17	$-CH_2-CH_2-O-\underline{H}$	17
7	$-C\underline{H}_2-CHO$	17
-	$-C\underline{H}_2-CH=NR$	20
10	$-CH_2-CH=N-O-\underline{H}$	17
31	$-N\underline{H}-CO-Ph$	15
30	$-N\underline{H}-CHO$	16
19	$-CH_2-C\underline{H}_2-NO_2$	13

In all these cases the cyclisation would lead to a tricyclic system that would represent the conjugate base of 1,2,3,4-tetrahydro-4-oxoquinazoline. By virtue of the fact that the excess charge on the N^1-nitrogen can be made available to

the carbonyl through the aromatic ring, such a system could be anticipated to have a pKa in the range of 18 to 20 and therefore it could be rationalised that those substituents whose pKa fall considerably above this value could undergo cyclisation readily, as with the cases of the 3-allyl and the 3-(2'-anilinoethyl)-3,4-dihydro-4-oxoquinazolines. Amongst those whose pKa could match that of the resulting tricyclic system is the 3-(2'-hydroxyethyl) and the 3-(2'-oximinoethyl) systems. The latter case is somewhat different, because of the necessity for the cyclisation to takeplace *via* the nitrogen. The 3-(2'-oxoethyl), the 3-(2'-iminoethyl), the 3-benzoylamino and the 3-formylamino fall into the category where cyclisation would lead to a conjugate base of lower stability, and therefore cyclisation may not be easily accomplished. Parenthetically, it may be recalled that the 3-(2'-oxoethyl) and the 3-(2'-iminoethyl) show a great tendency to exist in the tricyclic form 9 and 11 and their conjugate bases readily cause the rupture leading to the open forms. In sum, the substituted systems thus prepared and characterised consist of a selection of compounds that are amenable to cyclisation, those whose tendency for cyclisation could be considered marginal and those which could be predicted to be unfavourably disposed for cyclisation. Those falling into the last category can however be processed through the cycle *via* initial cleavage, followed by cyclisation, whereas all the

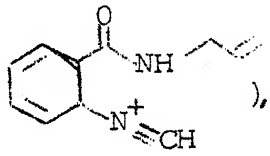
substituted systems can also, in principle, be cleaved first and then cyclised subsequently. It was envisaged that the requisite ligand conjugate bases that would lead to product ring conjugate bases of higher stability can be generated by reaction with organometallic compounds.

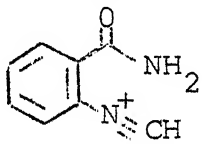
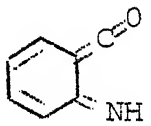
In spite of the great interest in the chemistry of quinazoline, there has been only scant studies pertaining to the reaction of organometallic compounds with 3-substituted 3,4-dihydro-4-oxoquinazolines. Indeed, the results thus far available do not match well, in the sense that in some cases, the Grignard reagent is believed to add to the 2-position and in some others to the carbonyl group itself[64]. Consequently, studies reported in the present work (vide infra) pertaining to the reactions of selected 3-substituted, 3,4-dihydro-4-oxoquinazolines with, largely, organolithium compounds have not only relevance to the problem at hand but also is of interest pertaining to the understanding of the behaviour of this class of compounds to N^3-substituted 3,4-dihydro-4-oxoquinazolines.

A detailed scrutiny of the reaction of 3-allyl-3,4-dihydro-4-oxoquinazoline (6) has been carried out to assess various possibilities. The reaction of 6 with PhLi followed by work up gave a 35% yield of 2-phenyl-3-allyl-1,2,3,4-tetrahydro-4-oxoquinazoline (54) and an 8% yield of 2-amino-N-allylbenzamide (55). It was further shown that brief heating of 54 followed by work up

gave quantitative yields of the open amino compound 55. Structural assignments for 54 and 55 is supported by spectral and analytical data. The observation that phenyllithium adds to the 3,4-dihydro-4-oxoquinazoline system without rupture of the ring is noteworthy, not only because it is a novel finding, but also because it demonstrated that the aminoacetal functionality present in such adducts are quite stable (CHART C.13).

54: mp. 129-30°C

Mass:m/e: 264 (M^+), 223 (M^+- .H_2C), 187 (),

147 (), 119 ()$^+$.

ir : ν_{max}(KBr) cm^{-1}: 3300 (NH), 1630 (amide carbonyl).

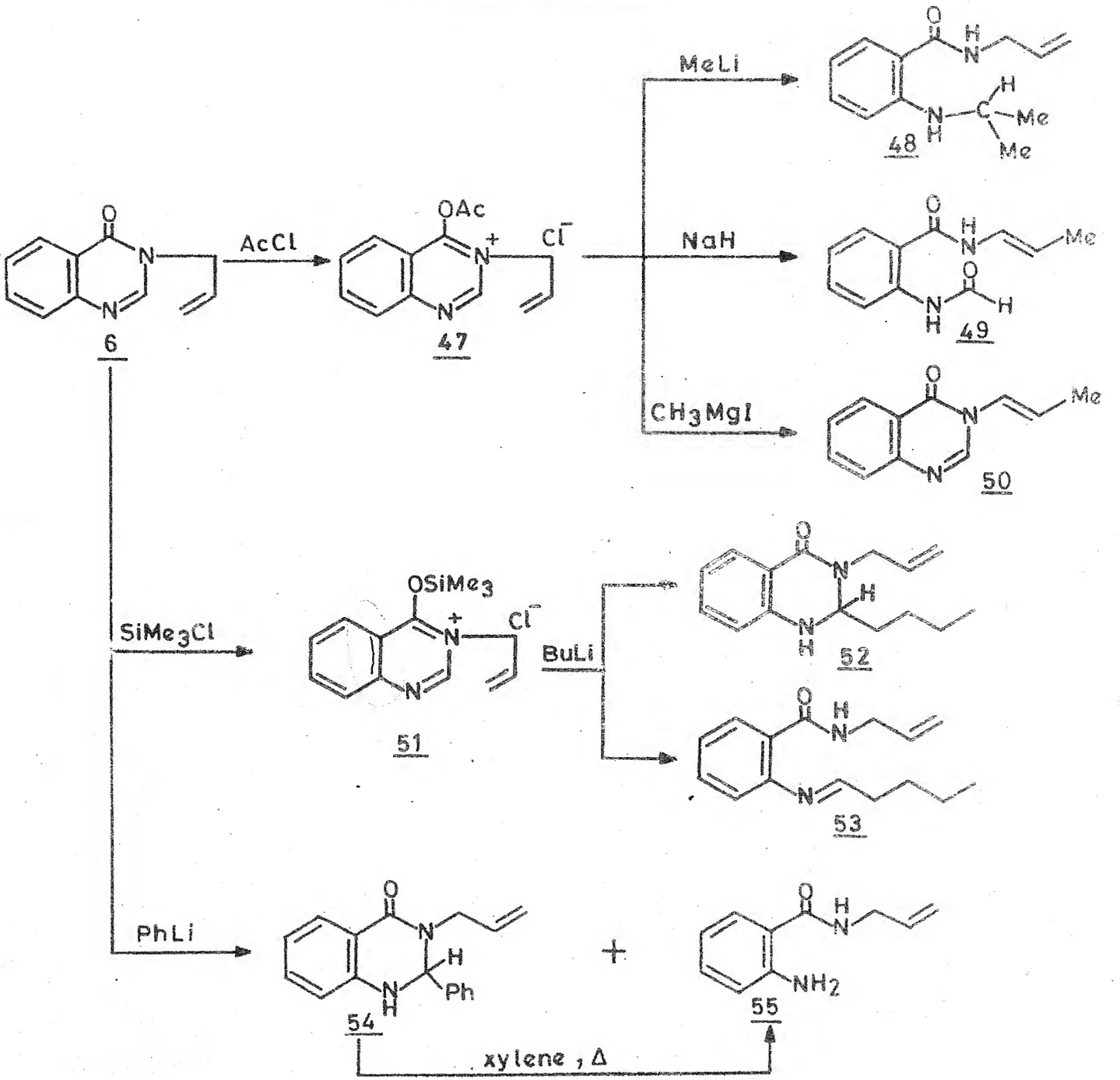
nmr: $\delta(CDCl_3)$ 60 MHz: 4.5-5.2 (m, 4H, -N-C<u>H</u>$_2$-, -CH=C<u>H</u>$_2$), 5.65 (d, 1H, -N-C<u>H</u>-Ø), 6.4 (m, 1H, 6'-quinazoline ring), 6.75 (dd, 1H, 6'-quinazoline ring), 7.0 (d, 1H, 7'-quinazoline ring), 7.2 (s, 5H, phenyl), 7.8 (d, 1H, 5'-quinazoline ring).

55: mp. 95-7°C

Mass:m/e: 176(M^+), 120 (M^+- .HN ), 92 (M^+-.HN-CO).

ir : ν_{max}(KBr) cm^{-1}: 3440, 3320 (NH_2), 1640 (amide carbonyl), 1620, 1590 (C=C).

CHART . C.13


MeLi
AcCl
NaH
CH3MgI
SiMe3Cl
BuLi
PhLi
xylene , Δ
6
47
48
49
50
51
52
53
54
55

nmr: $\delta(CDCl_3)$ 60 MHz: 4.0 (m, 2H, -N-$C\underline{H}_2$-), 5.2 (m, 2H, -CH=$C\underline{H}_2$), 6.0 (m, 1H, -$C\underline{H}$=CH_2), 6.3-7.3 (m, 4H, aromatic).

In endeavours to promote cyclisation over the addition to the 1-2 bond, compound 6 was converted to the 3-alkylated-4-acetoxy quinazolinium system 47 in excellent yields. The structural assignment for 47 is supported by spectral and analytical data (CHART C.13).

47: mp. (sinters at 120°C and melts at 145-50°C)

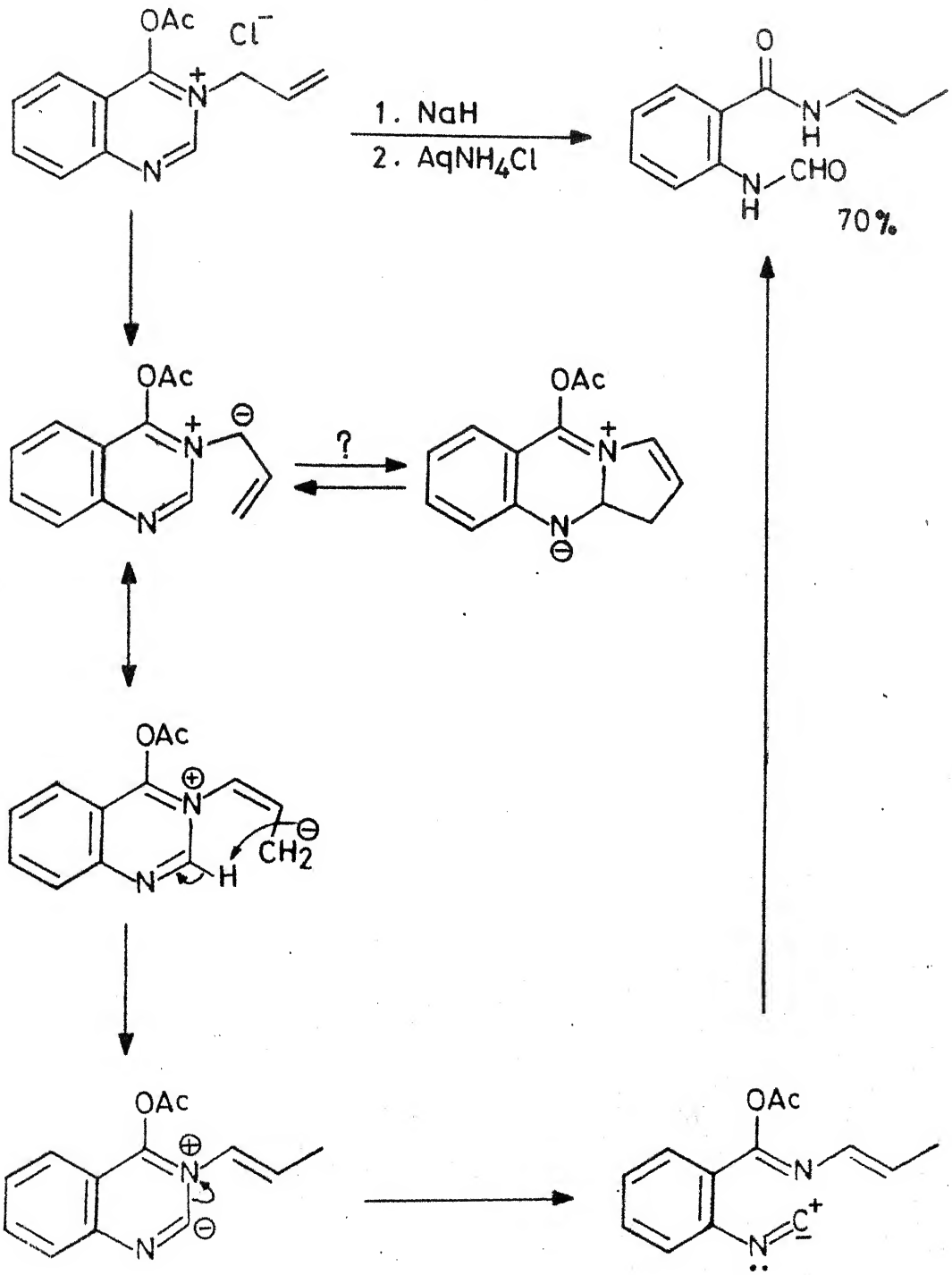
ir : ν_{max}(KBr) cm^{-1}: 2640 (br)(salt), 1715 (ester).

The reaction of the salt 47, with *in situ* generated MeLi gave rise to the bis methyllithium adduct 48 in 42% yield. The formation of 48 could be rationalised on the basis of the rapid addition of the elements of methyllithium to the 1-2 bond of 47, followed by rupture of the 2-3 bond, that would be highly favoured because of the charged nitrogen in the 3-position. Addition of a second unit of methyllithium to the Schiff base thus formed, followed by hydrolysis of the imino acetate function would give rise to 48. It was felt, that the cyclisation pathway would be more favourable, if the quinazolinium salt 47 were

to be treated with a reagent that is a strong base and at the same time a very ineffective nucleophile. In the event, surprisingly, the reaction of 47 with NaH led to the formation of the formamide derivative 49 in 70% yields. A particularly noteworthy feature of 49 is the migration of the terminal π in 47 to an internal one. The sequence of reactions leading to 49 in such good yields are rationalised on the basis of events described in CHART C.V. The expected conjugate base of 47 was most likely formed in the reaction, which could, in principle, because of the presence of the charged 3-nitrogen that could be anticipated to lower the pKa of the system considerably, exist in equilibrium with the expected tricyclic system. This equilibrium is disturbed *via* the irreversible process involving the open anion, namely the conjugate base of 47, which is quenched in an intramolecular manner *via* a six membered transition state, leading to the anion at the 2-position - entirely reasonable because of the charged nature of the quinazolinium system, which could undergo ready and irreversible ring rupture of the 2-3 bond, leading to an isocyanide and then under the conditions of work-up to 49.

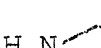
Yet another interesting reaction was the transformation of 47, to the 3-(1'-propenyl)-3,4-dihydro-4-oxoquinazoline (50) with CH_3MgI in 96% yields. It was anticipated that unlike CH_3Li the methyl - Grignard would show a decreased propensity for addition to the 1-2 bond and thus perhaps promote cyclisation of the conjugate base of 47. The isolation of 50, where the terminal

CHART C. V



π had migrated to an internal position, can be best explained by the formation of the expected conjugate base of 47. The absence of products in this case pertaining to the cleavage of the 2-3 bond along the lines illustrated for the 47 → 49 change can be rationalised on the conjugate base being co-valently bound to the Mg reagent (CHART C.13). The structural assignment for 48, 49 and 50 are supported by spectral and analytical data.

48: bp. 110°C/0.3 mm

Mass:m/e: 218 (M^+), 203 ($M^+-CH_3.$), 160 ($M^+-CH_3.-HN$ ), 146 ($M^+-CH_3.-H_2N$ ).

ir : ν_{max}(neat) cm^{-1}: 3340 (NH), 3090 (aromatic, olefinic CH), 2940, 2880 (saturated CH), 1630 (amide carbonyl), 1580, 1520 (secondary amide).

nmr: δ($CDCl_3$) 200 MHz: 1.1 (d, 6H, -CH-($C\underline{H}_3$)$_2$), 3.5 (sept, 1H, -C$\underline{H}$-(CH_3)$_2$), 3.86 (m, 2H, -N$\underline{H}$-C$\underline{H}_2$-), 5.1 (m, 2H, -CH=C$\underline{H}_2$), 5.8 (m, 1H, -C$\underline{H}$=CH_2), 6.22 (br, 1H, -N$\underline{H}$-CH_2-), 6.42 (t, 1H, 5'-anthranilic acid), 6.62 (t, 1H, 3'-anthranilic acid), 7.25 (d, 1H, 6'-anthranilic acid).

49: mp. 109-11°C

Mass:m/e: 204 (M^+), 186 (M^+-H_2O), 148 ($M^+-.HN$ ), 120 ($M^+-.HN$  $-CO$), 92 ($M^+-.HN$  $-2CO$).

ir : ν_{max}(KBr) cm^{-1}: 3300 (NH), 1670 (amide carbonyl), 1640, 1600 (C=C), 1580, 1525 (secondary amide).

nmr: δ ($CDCl_3$) 200 MHz: 1.63 (dd, 3H, -CH-$C\underline{H}_3$), 4.9 (q, 1H, =$C\underline{H}$-CH_3), 6.7 (m, 1H, -NH-$C\underline{H}$=CH-), 6.98 (t, 1H, 5'-anthranilic acid), 7.35 (m, 2H, 3',4'-anthranilic acid), 7.95 (d, br, 1H, -CO-$N\underline{H}$-CH-), 8.25 (d, 1H, -NH-$C\underline{H}$O), 8.38 (d, 1H, 6'-anthranilic acid).

50: mp. 61°C

Mass:m/e: 186(M^+), 177 (M^+-CH_3) base peak.

The quinazolinium salt 51 was prepared from 6 and trimethylsilyl chloride in quantitative yields. The structural assignment for 51 is supported by spectral data.

51: mp. 160°C

Mass:m/e: 186 (M^+-Me_3SiCl)

ir : ν_{max}(KBr) cm^{-1}: 2600 (br)(salt), 1610, 1580, 1550 (C=C, C=N), 960, 900 (Si-O).

The reaction of 51 with n-BuLi, gave products arising from addition of the organometallic reagent to the 1-2 bond, leading to the cyclic adduct 52 (16.5%) and the open chain analog 53

(17.5%) (CHART C.13). It may be noted that, whilst the acetyl salt gave, with organometallic reagents, compounds of a different nature compared to that from the precursor 6, that with the trimethylsilyl salt were quite similar. It is quite possible that this may be due to the prior desilylation of 51 → 6 followed by addition of n-BuLi. The structural assignment for 52 and 53 is supported by spectral data.

52: bp. 160°C/0.2 mm

ir : ν_{max}(neat) cm^{-1}: 3340 (NH), 2960, 2920, 2860 (saturated CH), 1690 (amide carbonyl), 1650, 1580 (C=C).

nmr: $\delta(CDCl_3)$ 60 MHz: 0.8-1.9 (m, 9H, butyl), 4.0 (m, 2H, -N-C<u>H</u>$_2$-), 5.2 (m, 2H, -CH=C<u>H</u>$_2$), 5.6-6.2 (m, 2H, -C<u>H</u>=CH$_2$, -C<u>H</u>-Bu), 7-7.6 (m, 4H, aromatic).

53: bp. 190°C/0.2 mm

ir : ν_{max}(neat) cm^{-1}: 3320 (NH), 2960, 2930, 2860 (saturated CH), 1640 br (amide carbonyl).

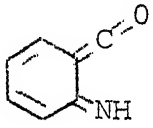
nmr: $\delta(CDCl_3)$ 60 MHz: 0.8-1.9 (m, 9H, n-butyl), 4.5 (m, 2H, -NH-C<u>H</u>$_2$-), 5.2 (m, 2H, -CH=C<u>H</u>$_2$), 5.9 (m, 1H, -C<u>H</u>=CH$_2$), 6.4-8.0 (m, 6H, aromatic, -N=C<u>H</u>-, -CO-N<u>H</u>-).

In the earlier reactions involving either the 3-allyl-3,4-dihydro-4-oxoquinazoline (6) or its salt, the involvement of the expected conjugate base, that is a prerequisite for cyclisation to the 2-position, was inferred in some cases. Thus, experiments have shown very clearly that there is a great tendency for systems such as 6 to undergo nucleophilic addition at the 2-location. This is very strongly re-inforced from studies relating to the reactions of such systems with hydroxide ions, where the addition to the 1-2 bond takes place with great ease (vide infra). It was therefore anticipated that a terminal O^- generated, must add to the 1-2 bond, provided the transition state is permissible. With this objective, the reaction of 2'-hydroxyethyl-3,4-dihydro-4-oxoquinazoline (17) was studied with PhLi as well as with n-BuLi. In both the cases, the isolated product were the simple adducts 56 (33%) and 57 (63%) respectively. Based on the properties of systems such as 17, it has to be concluded that, the conjugate base of 17 which must result via quenching process, should readily add to the 2-position of quinazoline, transferring the charge to the 1-nitrogen. It is clear from the results of experiments with 17, that the equilibrium favours the open oxygen anion and that the reaction proceeds in an irreversible manner, by the addition of elements of the organolithium compound to the 2-position. Thus, in this case also, the tricyclic system that could be related to the ATP-Imidazole Cycle was produced, but could not be made use of owing to its instability under the

conditions of the reaction. The structural assignment for 56 and 57 are supported by spectral and analytical data (CHART C.14).

56: mp. 115-6°C

Mass:m/e: 268(M^+), 208 (M^+-.HN-CH_2-CH_2-OH), 191(M^+-C_6H_5.),

119 ()$^+$.

ir : ν_{max}(KBr) cm^{-1}: 3400 (OH), 3320 (NH), 1620, 1610, 1580 (C=O).

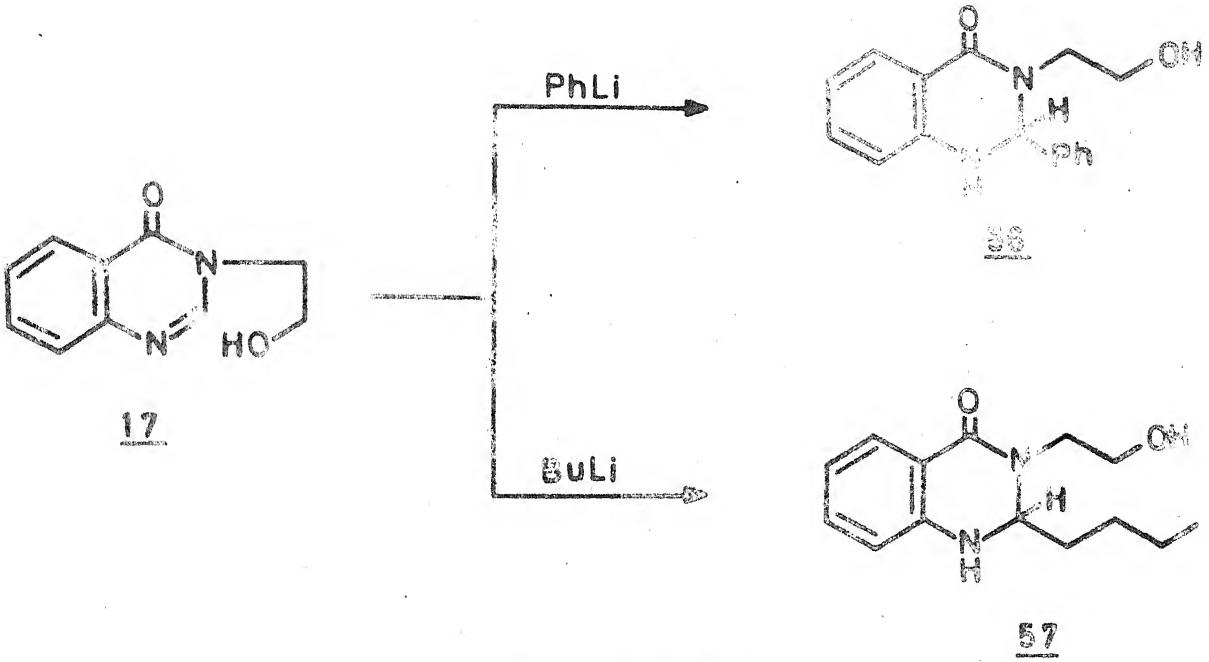
nmr: $\delta(CDCl_3)$ 60 MHz: 3.1 (m, 2H, -N-C<u>H</u>$_2$-), 3.6 (m, 2H, -C<u>H</u>$_2$-OH), 4.8 (br, 1H, -N<u>H</u>-), 5.8 (d, 1H, 2'-quinazoline ring), 6.4 (m, 1H, 8'-quinazoline ring), 6.8 (m, 1H, 6'-quinazoline ring), 7.1 (m, 1H, 7'-quinazoline ring), 7.3 (s, 5H, phenyl), 7.85 (dd, 1H, 5'-quinazoline ring).

57: mp. 94-5°C

ir : ν_{max}(KBr) cm^{-1}: 3300 (br)(OH,NH), 2950, 2800 (saturated CH), 1630, 1570 (C=O).

nmr: $\delta(CDCl_3)$ 500 MHz: 0.86 (t, 3H, -C<u>H</u>$_3$), 1.25 (m, 4H, -C<u>H</u>$_2$-C<u>H</u>$_2$-CH_3), 1.65, 1.85 (m,m, 2H, -CH-C<u>H</u>$_2$-), 3.18 (br, 1H, -CH_2-O<u>H</u>), 3.63 (br, 1H, -N<u>H</u>-CH_2-), 3.8 (m, 2H, -N-C<u>H</u>$_2$-CH_2-), 4.0 (m, 1H, 2'-quinazoline

CHART. C.14

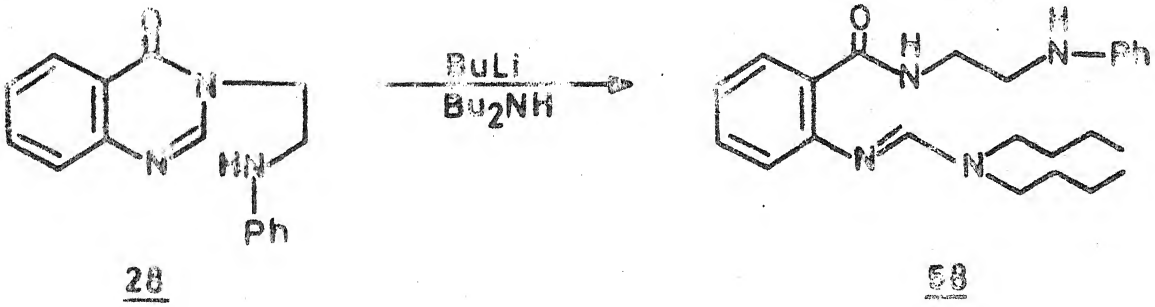


17

38

57

CHART. C.15



28

58

ring), 4.65 (m, 2H, -C$\underline{H}_2$-OH), 6.65 (d, 1H, 8'-quinazoline ring), 6.84 (t, 1H, 6'-quinazoline ring), 7.25 (m, 1H, 7'-quinazoline ring), 7.85 (d, 1H, 5'-quinazoline ring).

To assess the proclivity of the quinazolone system for addition to the 1-2 bond, a competition experiment was planned, using 3-(2'-cyanoethyl-3,4-dihydro-4-oxoquinazoline (26) as the substrate. In this, the result should reflect the tendency towards addition to the 1-2 bond of quinazolone against 1,2 addition to the nitrile function. In the latter case, the resulting electron excess system created at the nitrogen could lead to cyclisation, that would offer a method for the template mediated synthesis of 6-membered heterocyclic system. In the event, however, when 26 was reacted with PhLi, 65.5% of 3,4-dihydro-4-oxoquinazoline 2 arising from a retro-Michael reaction was obtained. This clearly demonstrates the formation of the conjugate base at the 2'-position, where the organometallic reagent performed the function of a base. Of interest, however, was the formation of, in 18.5% yield, 2-phenyl-1,2,3,4-tetrahydro-4-oxoquinazoline (59) resulting from prior 1,2 addition to the quinazolone system, since compound 2 formed by retro-Michael process would immediately form the conjugate base with PhLi, thus totally precluding the addition to the 1-2 bond. Therefore, the results

of the reaction of 26 with PhLi gives a fair assessment of three different processes that are possible. It is clear that the retro-Michael reaction is preferred. The next important pathway is the addition of elements of PhLi which on retro-Michael would lead to 59. The structural assignment to 59 is supported by spectral and analytical data and on comparison with properties of the substance prepared in a different manner in the literature[66] (CHART C. 16).

59: mp. 228°C

Mass:m/e: 224(M^+), 147 ($M^+-C_6H_5\cdot$), 120 ($M^+-C_6H_5\cdot$-HCN), 92 ($M^+-C_6H_5\cdot$-HCN-CO).

ir : ν_{max}(KBr) cm^{-1}: 3300, 3200 (NH), 1670 (amide carbonyl), 1620, 1510 (C=C).

nmr: δ(DMSO-d_6) 500 MHz: 5.72 (m, 1H, -NH-C<u>H</u>-NH-), 6.5-7.65 (m, 10H, aromatic, -N<u>H</u>-CH-Ph), 8.22 (d, 1H, -CO-N<u>H</u>-CH-).

As stated earlier, pKa considerations would make 3-(2'-anilinoethyl)-3,4-dihydro-4-oxoquinazoline (28) a good substrate for cyclisation to the tricyclic system. In the event, however, reaction of 28 with the *in situ* generated Li-di-n-butylamide gave a complex mixture from which 26% of the unusual hetero system 58,

resulting from addition of the Li-di-n-butylamide unit to the 1-2 bond followed by rupture was obtained. Here again, it is rationalised that the conjugate base of 28 was indeed generated and that it formed an equilibrium mixture with the corresponding tricyclic anion by intramolecular addition to the 1-2 bond. This equilibrium which is anticipated to be in favour of the tricyclic system, is disturbed by the irreversible addition of Li-di-n-butylamide to the 1-2 bond and subsequent rupture of the 2-3 bond leading to the open system. The structural assignment for 58 is supported by spectral data (CHART C.15).

58: Syrup

ir : ν_{max}(KBr) cm^{-1}: 3350 (NH), 2960, 2920, 2860 (saturated CH), 1670 (amide carbonyl).

nmr: $\delta(CDCl_3 + DMSO\text{-}d_6)$ 60 MHz: 0.6-1.7 (m, 14H, $-CH_2-CH_2-CH_3$ x 2), 3.2 (m, 6H, $-N-CH_2$ x 2, $-CH_2-NH-\emptyset$), 3.55 (t, 2H, $-CH_2-CH_2-NH-\emptyset$), 6.2-8.2 (m, 5H, aromatic, $-N=CH-N$).

In most of the reactions discussed above, it is concluded that the expected tricyclic systems were indeed produced, but these systems always existed in equilibrium with the open partners. Whilst, strain, steric and stereo electronic factors

would not favour the rupture of the 2-3 bond in the tricyclic systems, such a process is greatly favoured in the open systems. This factor has made efforts to isolate the tricyclic products arising from cyclisation, infructuous. Several other endeavours to bring about either cyclisation or the transformation of the 3-alkylated quinazolones to further useful subtrates are worthy of passing mention. Attempted cyclisation of 3-allyl-3,4-dihydro-4-oxoquinazoline (6) to the tricyclic system, which *via* a cyclic operation could give rise to the daughter product pyrrole and the parent anthranilic acid, with acetic anhydride, trifluoroacetic acid, BF_3-etherate and HBr led to recovery of the starting material. It was felt that the desired cyclisation can be promoted by activation of the 1-nitrogen. To this end 6 was reacted with either $NaNO_2$-mineral acid that could have resulted in the nitrosation of 1-position or with peracids that could have led to the N^1-oxide. In both cases the starting material was recovered. Attempted cyclisation *via* mercuric acetate activation also failed. The readily available 2',2'-diethoxyethyl-3,4-dihydro-4-oxoquinazoline 8 was reacted with peracetic acid with the expectation that this would lead to the concomitant formation of N^1-oxide-aldehyde that could undergo cyclisation and *via* further pathways in the cycle to oxazole. In the event, the starting material was recovered. Similar results were obtained with $NaNO_2$-hydrochloric acid on 8. The oxime 10 was then considered as a possible substrate for further compounds relating to

the cycle. It was envisaged that the reduction of the oxime to the corresponding hydroxylamine could lead to the generation of the conjugate base of the hydroxylamine. It is known that such conjugate bases are very powerful nucleophiles and they exhibit this property *via* the nitrogen lone pair, eventually giving rise to N-hydroxy compounds. In the event, however, the reaction of oxime **10** with either sodium amalgam or lithium aluminium hydride failed. Another strategy that was attempted was the dehydration of 3-(2'-oximinoethyl)-3,4-dihydro-4-oxo-quinazoline (**10**) to the corresponding nitrile,namely, 3-cyano-methyl-3,4-dihydro-4-oxoquinazoline *via* dehydration. It was felt that this would be an attractive compound for further processing along the cycle, since, it could be readily seen that nucleophilic addition to the nitrile function followed by cyclisation and cleavage could lead to 2-substituted imidazoles, with the regeneration of the template anthranilic acid. Attempted dehydration of the oxime **10** with acetic anhydride or p-toluenesulphonyl-chloride or triphenylphosphine-triethylamine in carbontetra-chloride did not succeed. Finally attempted cyclisation of the conjugate base of oxime **10** that could eventually lead to N-hydro-xypyrroles, by treatment of **10** with either morpholine or sodium methoxide also led to the recovery of the starting material. The ready tendency of 3-(2'-oxoethyl)-3,4-dihydro-4-oxoquinazoline(**7**) to exist either as the hydrate or as ammonia adduct has been commented upon earlier. It was felt, that the ammonia adduct **11**,

for which the tricyclic structure 11 has been proposed, could be further processed along the cycle to lead to imidazole and anthranilic acid *via* removal of the hydroxy group as a better leaving group. To this effect compound 11 was treated with reagents such as aceticanhydride-pyridine, $TiCl_3$-pyridine, thermolysis in xylene, treatment with trifluoroacetic acid, treatment with HCl, reaction with NaH in DME and in a two phase system with anhydrous K_2CO_3. In all these cases, the product obtained was the aldehyde 7.

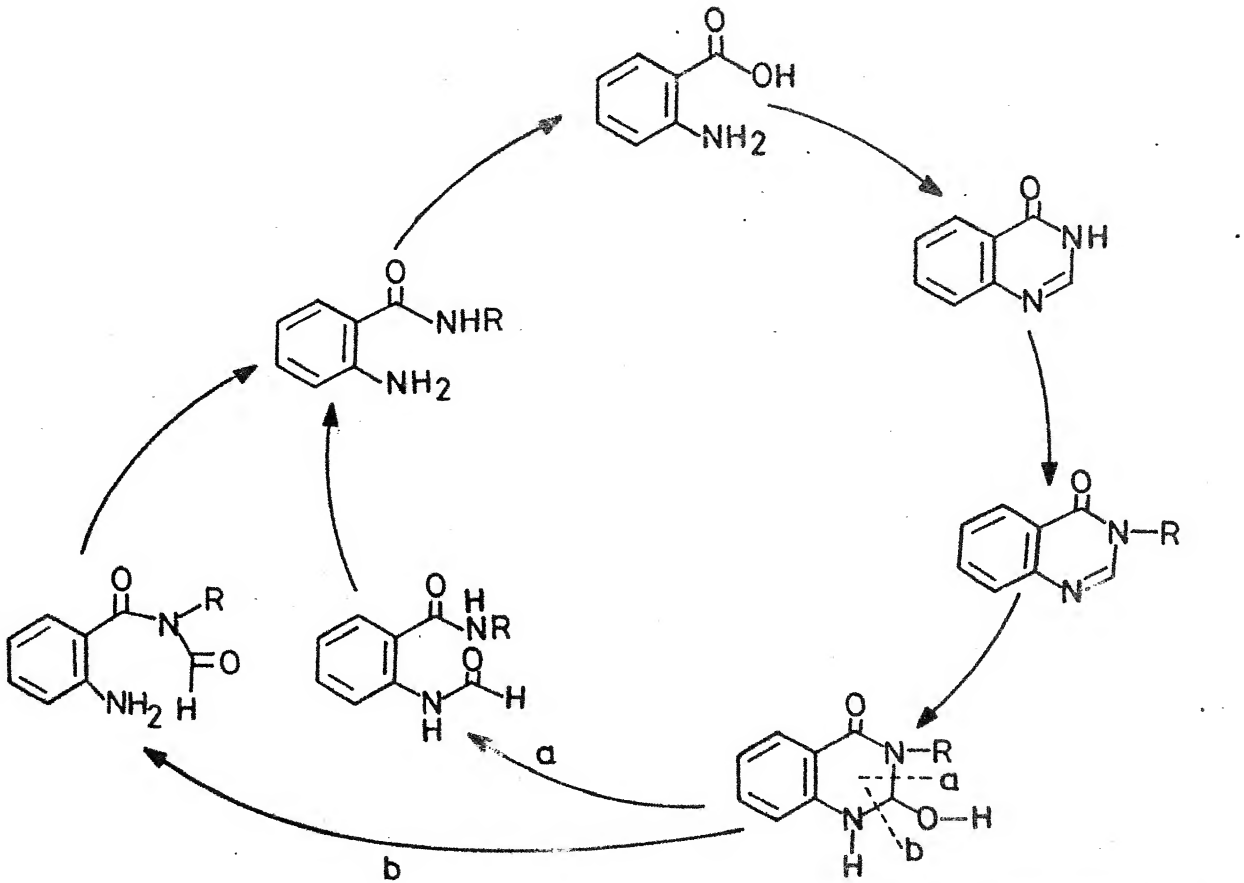
Endeavours to rupture the 1-2 bond of the specifically 3-substituted-3,4-dihydro-4-oxoquinazoline (TABLE C.I) was also simultaneously carried out. It was pointed out earlier, that, with reference to the chemical siumulation of the salient features of the ATP-Imidazole Cycle, the second stage is flexible (CHART C.III). Thus, specific cleavage of the 1-2 bond, followed by cyclisation, could lead to results identical to that, wherein, the pathway followed is cyclisation followed by 1-2 bond rupture.

A number of reports are available in literature[67] relating to the action of dilute alkali on systems similar to that presented in Table C.I. Excepting in rare cases, mostly belonging to the 2-substituted category, the results of such dilute alkali hydrolysis do not give information relating to which of the two bonds, namely, the 1-2 or the 2-3, is initially ruptured, since, the product isolated was either anthranilic acid or substrates

where the 2-carbon had disappeared ! It may be noted, that either 1-2 or 2-3 rupture would give rise to an additional amide unit, which could be further cleaved, generating the NH function. In early experiments involving treatment of the 3-substituted quinazolones prepared in this work, with dilute alkali, gave, most gratifyingly anthranilic acid which atleast amounted to the recovery of the parent. A detailed analysis of such reactions soon brought out the uncertainities associated with the formation of anthranilic acid. As stated earlier and illustrated in CHART C.VI, alkali can cleave either the 1-2 or the 2-3 bond. The desired 'b' type cleavage will keep the required 2-3 bond intact, in contrast to the 'a' type cleavage which is of no use relating to the further transformations of the cycle. All the evidence with 3-substituted-3,4-dihydro-4-oxoquinazolines with dilute alkali are in more agreement with the 'a' type cleavage (CHART C.VI).

The readily available 3-allyl-3,4-dihydro-4-oxoquinazoline (6) was the natural choice for preliminary studies related to cleavage with dilute alkali. Reaction of 6 with 1N NaOH, followed by benzoylation of the reaction mixture, gave, the di-amide 60 (17%) and 2-phenyl-3,1(4H)-benzoxazone (61) (27.5%) and benzoyl-anthranilic acid (65) (43%) the latter arising from benzoylation of the anthranilic acid produced in the reaction. It was also shown that the hydrolysis product 60 could be completely cleaved

CHART C.VI



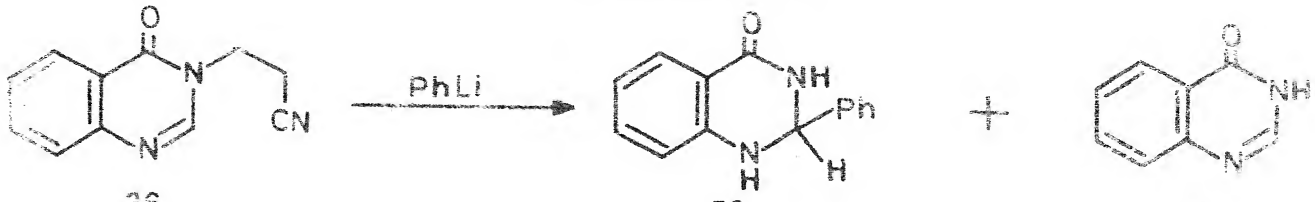
R = — CH_2–CH$(OEt)_2$

= — CH_2–CH= CH_2

= — NH—COPh

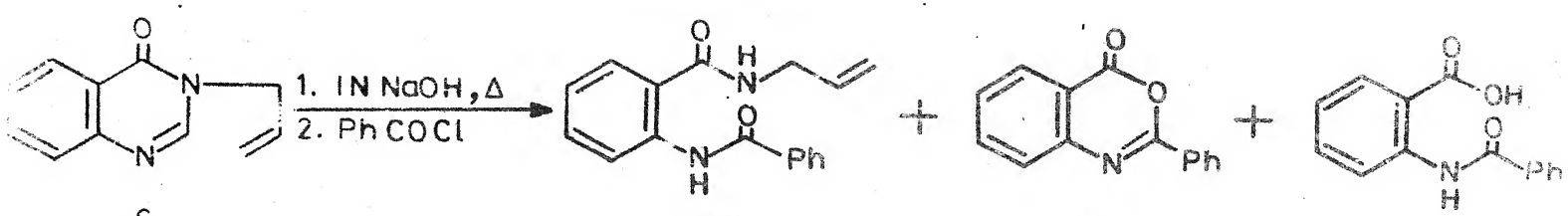
to anthranilic acid (1) with aqueous alkali. The structural assignment for 2-phenyl-3,1(4H)-benzoxazone (61), whose formation is rationalised on the basis of the formation of the mixed anhydride between 65 and benzoyl chloride followed by cyclisation and loss of elements of benzoic acid, was confirmed by preparation of authentic sample from N-benzoylanthranilic acid[68] and acetic anhydride. The formation of 60 is a result of the cleavage giving rise to authranilic acid allyl amide, which, in principle, could arise either by 1-2 cleavage, that would give rise to N-formyl anthranilic acid allylamide or by 2-3 cleavage leading to N-formylanthranilic acid 62. Since compound 62 could be readily prepared from anthranilic acid and formic acid[69], its involvement *in situ* could be demonstrated by treatment with aqueous hydroxide under conditions described above. In the event, treatment of 62 with aqueous hydroxide led to the formation of anthranilic acid in excellent yields. This experiment would only show that the N-allylamide of anthranilic acid, the cleavage product of 6 with hydroxide could arise either by 1-2 or by 2-3 cleavage. It may be noted that the 2-3 cleavage product would result in a bis amide which will be very highly susceptible for further hydrolysis. Since, 2-phenyl-3,1(4H)-benzoxazone arises from anthranilic acid produced by the cleavage, the extent of anthranilic acid formation comes to 70.5%. The structural assignment for 60 and 61 is supported by spectral and analytical data (CHART C.17, C.18 and C.19).

CHART . C . 16



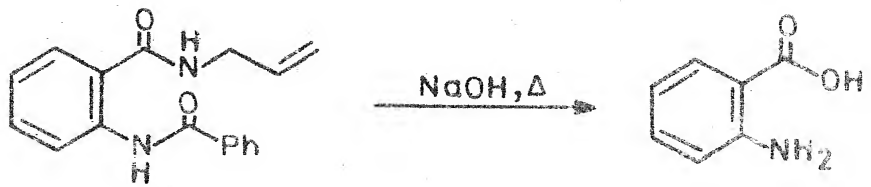
26 59 2

CHART . C . 17



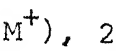
6 60 61 65

CHART . C . 18



60 1

60: mp. 95-6°C

Mass:m/e: 280 (M^+), 224 (M^+-.HN ), 203 ($M^+-C_6H_5$.), 196 (M^+-.HN  -CO), 175 ($M^+-C_6H_5CO$.).

ir : ν_{max}(KBr) cm^{-1}: 3360 (NH), 1650 (amidecarbonyl), 1600, 1590, 1520 (C=C, secondary amide).

nmr: $\delta(CDCl_3)$ 200 MHz: 4.15 (t, 2H, -N-C<u>H</u>$_2$-), 5.3 (m, 2H, -CH=C<u>H</u>$_2$), 5.95 (m, 1H, -C<u>H</u>=CH$_2$), 6.7 (s, br, 1H, -CO-N<u>H</u>-CH$_2$-), 7.1 (t, 1H, 5'-anthranilic acid), 7.35 (m, 6H, 3,4,5-phenyl, 3',4'-anthranilic acid, -N<u>H</u>-CO-Ø), 8.1 (d,d,2H, 2,6-phenyl), 8.7 (d, 1H, 6'-anthranilic acid).

61: mp. 123-4°C

ir : ν_{max}(KBr) cm^{-1}: 1760 (lactone), 1610, 1565 (C=C, C=N).

nmr: $\delta(CDCl_3)$ 200 MHz: 7.55 (q, 4H, 2,3,5,6-phenyl), 7.75 (d, 1H, 4-phenyl), 7.85 (dd, 1H, 8'-benzoxazone ring), 8.25 (dd, 1H, 5'-benzoxazone ring), 8.35 (dd, 2H, 6',7'-benzoxazone ring).

As anticipated, the cleavage of the 6-nitro-3-allyl-3,4-dihydro-4-oxoquinazoline (<u>14</u>), could be brought about under much milder conditions using 0.5N NaOH. The sole product that

could be isolated was 5-nitroanthranilic acid[70] (63) in 95% yields (CHART C.20).

The reaction of 2,2 -diethoxyethyl-3,4-dihydro-4-oxo-quinazoline (8) with aqueous sodium hydroxide under reflux, followed by benzoylation of the resulting reaction mixture, gave rise to the amidoacetal (64) (82.5%) and N-benzoylanthranilic acid (57.2%), arising from benzoylation of the corresponding amines, 2,2-diethoxyethylamine (aminoacetaldehyde diethylacetal) and anthranilic acid. The structural assignment for 64 is supported by spectral and analytical data and that for 65 by comparison with authentic sample (CHART C.21). This cleavage, although of no use pertaining to further processes related to the cycle, offers an advantageous method for the preparation of sensitive amino compounds such as those related to 64.

65: mp. 274°C

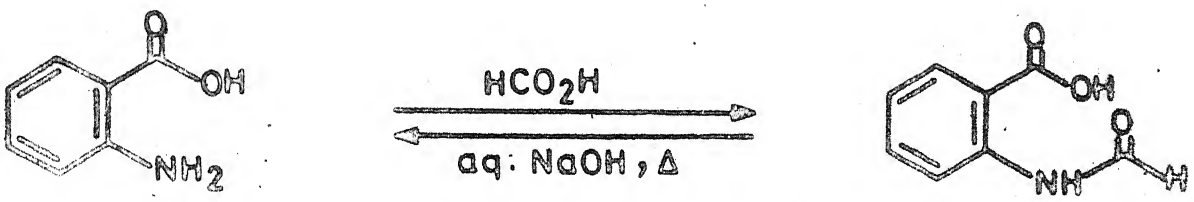
64: bp. 115°C/0.25 mm

Mass:m/e: 191 ($M^+-C_2H_5OH$).

ir : ν_{max}(neat) cm^{-1}: 3345 (NH), 1660 (amide carbonyl), 1605, 1580, 1550 (C=C, secondary amide).

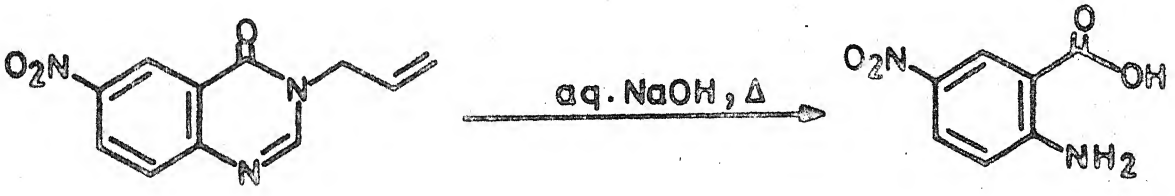
nmr: $\delta(CDCl_3)$ 60 MHz: 1.15 (t, 6H, $-CH_2-\underline{CH_3}$x2), 3.5 (m, 6H, $-\underline{CH_2}-CH_3$x2, $-NH-\underline{CH_2}-$), 4.55 (t, 1H, $-CH_2-\underline{CH}$), 6.55 (br, 1H, $-CO-\underline{NH}-$), 7.1-7.8 (m, 5H, aromatic).

CHART. C.19



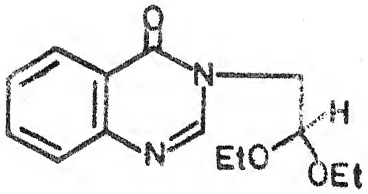
1 62

CHART. C.20



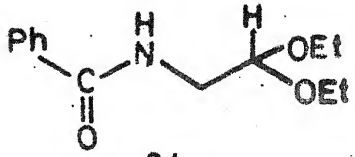
14 63

CHART . C.21



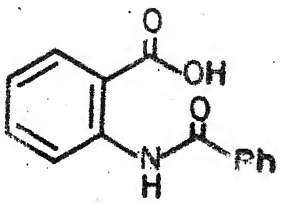
8

1 . aq. NaOH, Δ
2 . PhCOCl



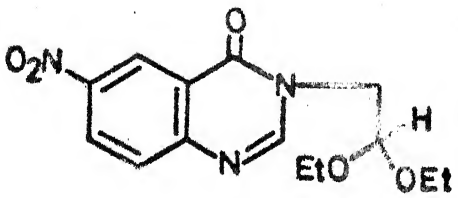
64

+



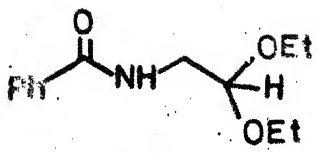
65

CHART . C.22



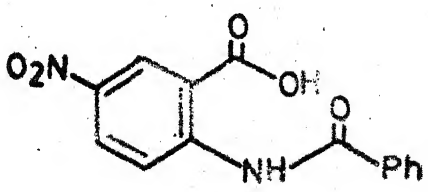
15

aq. NaOH
PhCOCl



64

+



63 a

As anticipated, the, 6-nitroanalog of 8, namely 15, underwent cleavage with dilute alkali under relatively mild conditions giving rise to, after benzoylation, compound 64 (86.5%) and a much better yield of 5-nitro-N-benzoylanthranilic acid (63a)[71] (78%). No other product could be isolated (CHART C.22).

63a: mp. 255°C

The reaction of 3-(2'-nitroethyl)-3,4-dihydro-4-oxoquinazoline (19) with aqueous alkali followed by benzoylation gave, as the sole isolable product, 2-phenyl-3,1(4H)-benzoxazone (61) in 61% yields.

It was mentioned earlier, that on the basis of pKa considerations, the compound 3-benzoylamino-3,4-dihydro-4-oxoquinazoline (31) could be placed in the cycle by prior cleavage of the 1-2 bond followed by cyclisation and rupture. In the event, the reaction of 31 with aqueous hydroxide gave an 18% yield of o-aminobenzoyl hydrazine (66), an 8% yield of 1-benzoyl-2-o-aminobenzoyl hydrazine (67) and a 73% yield of anthranilic acid. The formation of these compounds could again be explained on the basis of either the 1-2 or the 2-3 cleavage, since, here also, the 2-carbon has been removed. It was also shown that the anthranilic acid benzoylhydrazide 67 could be readily hydrolysed

to anthranilic acid. The structure of 66 was confirmed by comparison with authentic sample prepared from methyl anthranilate and hydrazine[72] (CHART C.24).

66: mp. 123°C

ir : ν_{max}(KBr) cm^{-1}: 3440, 3320 (NH_2), 1650 (amide carbonyl), 1620, 1580 (C=C).

nmr: δ(DMSO-d_6) 500 MHz: 6.22 (s, 4H, CONH-N<u>H</u>$_2$, -C_6H_4-N<u>H</u>$_2$), 6.4 (t, 1H, 5'-anthranilic acid), 6.62 (d, 1H, 3'-anthranilic acid), 7.05 (t, 1H, 4'-anthranilic acid), 7.73 (d, 1H, 6'-anthranilic acid), 9.4 (s, 1H, -CO-N<u>H</u>-).

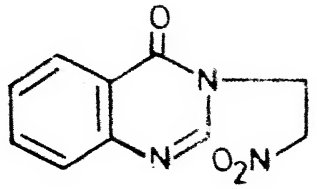
67: mp. 178°C

Mass:m/e: 255 (M^+)

ir : ν_{max}(KBr) cm^{-1}: 3400, 3280 (br, NH_2), 1650 (amide carbonyl), 1620, 1575 (C=C).

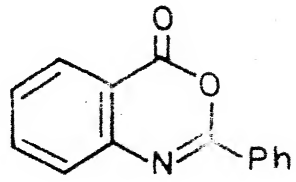
nmr: δ(DMSO-d_6) 500 MHz: 6.3 (s, 2H, -N<u>H</u>$_2$), 6.42 (t, 1H, 5'-anthranilic acid), 6.65 (d, 1H, 3'-anthranilic acid), 7.18 (t, 1H, 4'-anthranilic acid), 7.48 (t, 2H, 3,5-phenyl), 7.55 (d, 1H, 4-phenyl), 7.6 (d, 1H, 6'-anthranilic acid), 7.9 (d, 2H, 2,6-phenyl), 10.2 (br, 2H, -N<u>H</u>-N<u>H</u>-).

CHART . C 23



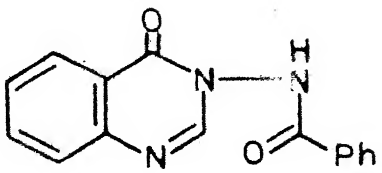
19

1. aq NaOH, Δ
2. PhCOCl



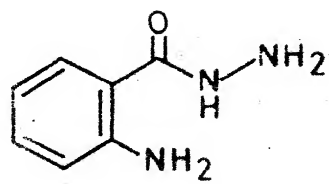
61

CHART . C.24



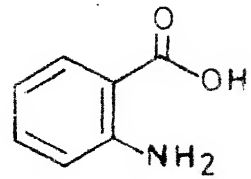
31

aq . NaOH
Δ



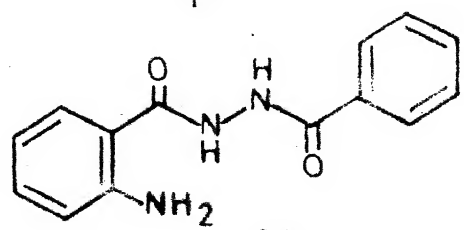
66

+



1

+



67

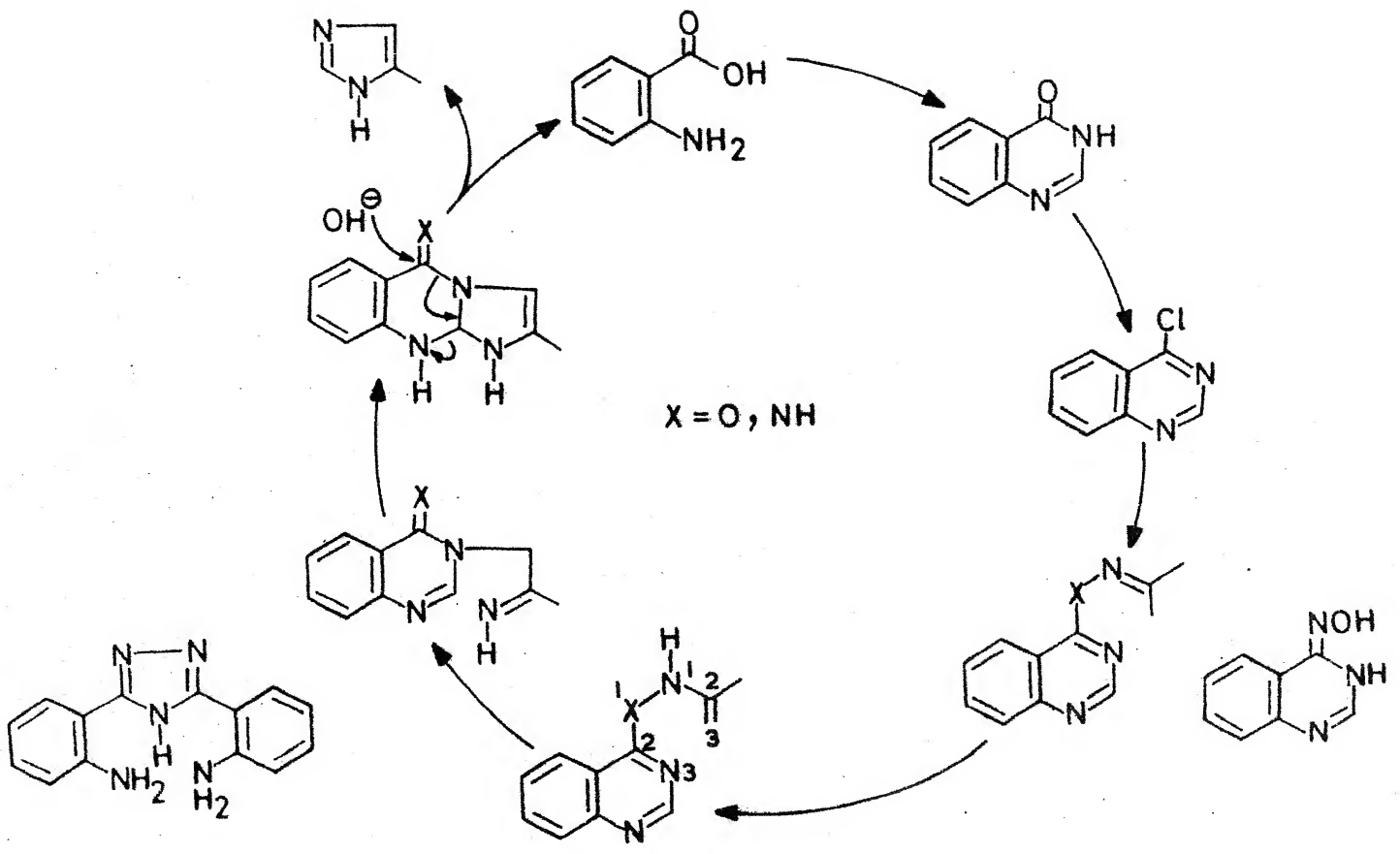
NaOH
Δ

The aqueous alkali rupture of 3-substituted 3,4-dihydro-4-oxoquinazolines has not given products that could be processed on the cycle. Also, no definite conclusions could be arrived at, relating to which of the two bonds, namely, 1-2 or 2-3 undergoes the initial cleavage.

The [3,3] shift in the quinazoline and purine series was taken advantage of, as described earlier, for the preparation of specifically N-alkylated compounds of relevence to the cycle.

It was envisaged that such a strategy could also lead to specifically N-alkylated products that can undergo further transformations, under the conditions of the reaction, along the desired cycle, progressing even to the generation of the template and the product ! These expectations are ellustrated in CHART C.VII, with 3,4-dihydro-4-oxoquinazoline 2, derived from the model template anthranilic acid, as the substrate. The same sequence of reactions are also possible with hypoxanthine 34, readily available from the template molecule 5-aminoimidazole-4-carboxamide. It could be readily seen from CHART C.VII that the initially formed [3,3] shift product, derivable either from the oxime ethers (X=O) or hydrazones (X=NH), related to either the quinazolone 2 or the hypoxanthine 34, could undergo further cyclisations readily, and the resulting tricyclic systems could be further transformed to the parent template and the daughter imidazole. In the case of such [3,3] transformations with

CHART C.VII



hydrazones (X=NH) the tricyclic systems arising from cyclisation of the primary [3,3] shift, could undergo further fragmentation to the daughter imidazole with the concomitant generation of the carbonyl function of the template as a nitrile equivalent. In the case of oxime ethers (X=O) as well as with hydrazones (X=NH) such tricyclic systems could be hydrolytically transformed to the daughter imidazoles and the parent templates.

4-chloroquinazoline (4), readily preparable from 3,4-dihydro-4-oxoquinazoline (2), on treatment with the conjugate base of acetone oxime gave the expected oxime ether 74 in 90% yields. The structural assignment for 74 is supported by spectral and analytical data (CHART C.27).

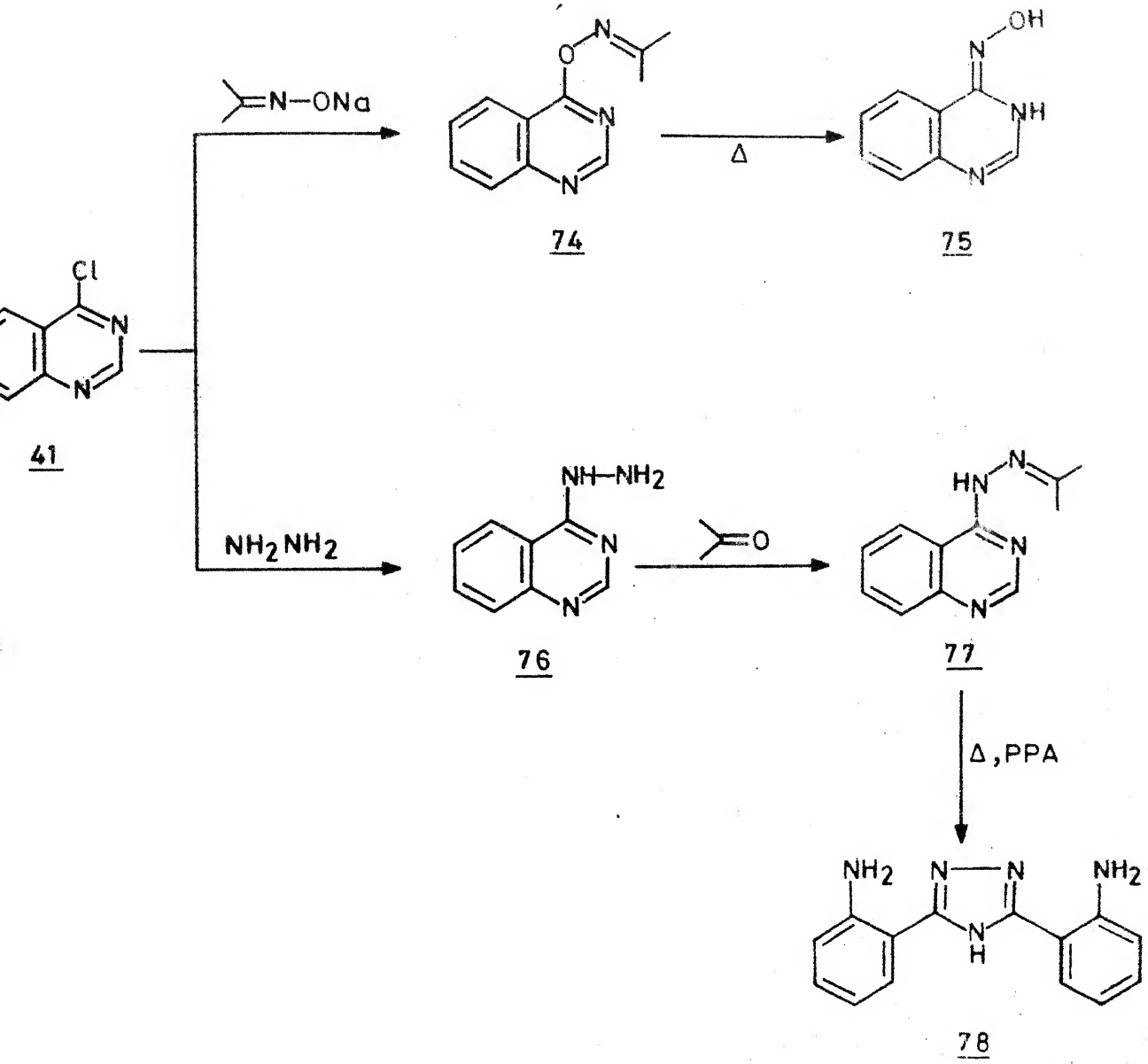
74: viscous liquid

ir : ν_{max}(neat) cm^{-1}: 1620, 1570 (C=C, C=N).

nmr: $\delta(CDCl_3)$ 60 MHz: 1.95 (s, 6H, $-N=C(CH_3)_2$), 7.1-8.0 (4H, 5',6',7',8'-quinazoline ring), 8.66 (s, 1H, 2'-quinazoline ring).

Neat thermolysis of 74 gave, as the sole isolable product, a colourless crystalline compound mp. 205°C which has been assigned structure 75 (20%) on the basis of spectral data. The formation of 75 can be rationalised as shown in CHART C.VIII, via

CHART . C . 27


Cl
N
N
41
=N–ONa
O
N
N
74
Δ
OH
N
NH
N
75
NH–NH2
NH2NH2
N
N
76
=O
HN
N
N
77
Δ, PPA
NH2
N
N
NH2
N
H
78

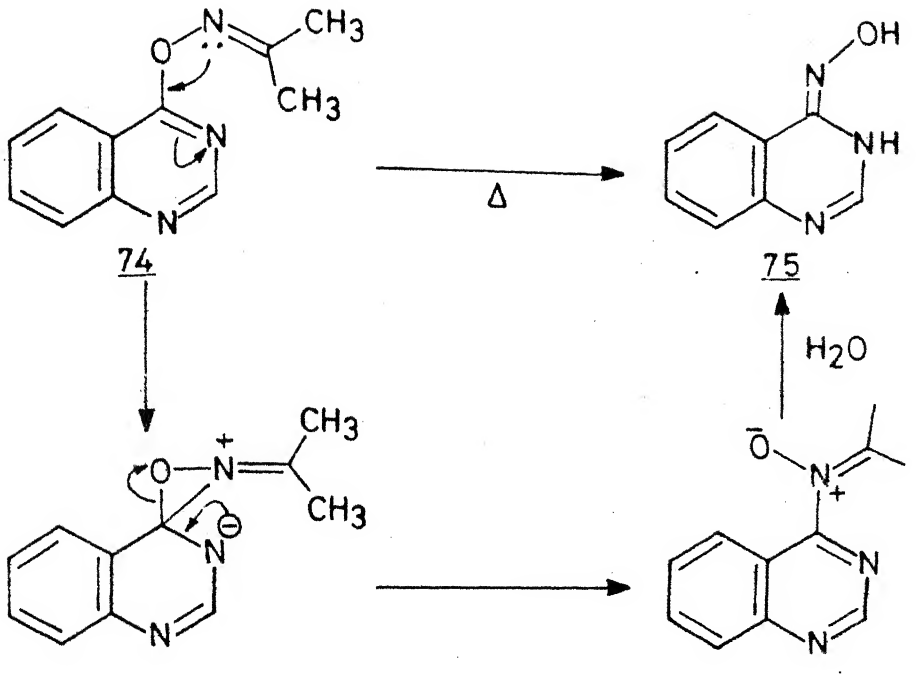
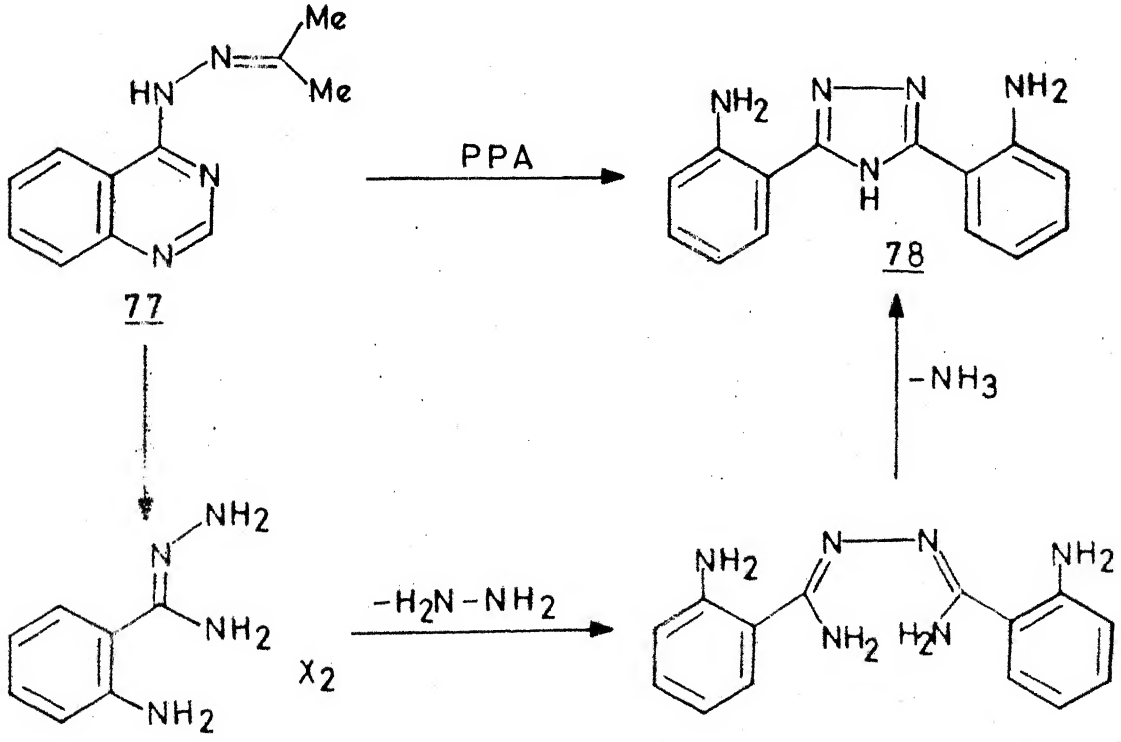

CH3
CH3
O
N
N
N
74
Δ
OH
N
NH
N
75
H2O
CH3
CH3
O
N
N
N
O
N
N
N

CHART C.IX


Me
N
HN
Me
N
N
77
PPA
NH2
N
N
NH2
N
H
78
-NH3
NH2
N
NH2
NH2
X2
-H2N-NH2
NH2
N
N
NH2
NH2
NH2
H2N

participation of the highly reactive nitrogen lone pair of the oxime ether generating electron excess at the 3-position of the quinazoline ring, which, in turn, ruptures the fragile oxirane system thus produced giving rise to a nitrone, that could be expected to undergo ready hydrolysis to acetone and 75 (CHART C.27).

75: mp. 205°C

Mass:m/e: 161 (M^+)

ir : ν_{max}(KBr) cm^{-1}: 3340 (NH), 1685 (C=N-OH), 1585, 1560, 1520 (C=C, C=N).

nmr: δ (DMSO-d_6) 500 MHz: 7.48 (m, 1H), 7.63 (t, 1H), 7.76 (m ,2H), 8.1 (m, 2H), 8.32 (s, 1H).

In a parellel series of experiments 4-chloroquinazoline(4) was converted to 4-hydrazinoquinazoline[73] in 80% yields, which, on treatment with acetone gave the hydrazone[74] 77 (95% yield). The structural assignment for 76 and 77 is supported by spectral data (CHART C.27).

76: mp. 185-6°C

ir : ν_{max}(KBr) cm^{-1}: 3320, 3200 (NH_2), 1640, 1620, 1580 (C=C, C=N).

77: mp. 174-5°C

ir : ν_{max}(KBr) cm^{-1}: 3100 (NH), 1615, 1560 (C=C, C=N).

The hydrazone 77 was treated with polyphosphoric acid under conditions normally employed for the Fischer-Indole rearrangement. Careful analysis of the resulting complex mixture gave a 39% yield of 3,4-dihydro-4-oxoquinazoline (2) and a crystalline compound mp. 205-6°C which has been assigned the bis-2,5-o-aminophenyltriazole structure 78 (9.65%). The formation of 78 is rationalised in CHART C.IX. As with many examples presented earlier, the hydrazone 77 could readily lose the 2-carbon position of the quinazoline, giving rise to an amide hydrazone. Two of such units could condense with loss of elements of hydrazine and the resulting dimer on cyclisation with loss of ammonia could give rise to 78 (CHART C.27).

78: mp. 205-6°C

Mass:m/e: 251 (M^+)

ir : ν_{max}(KBr) cm^{-1}: 3460, 3400, 3340 (NH_2), 1610, 1575, 1550 (C=C, C=N).

nmr: δ(DMSO-d_6) 500 MHz: 6.64 (t, 2H, 5'-ring), 6.81 (d, 2H, 3'-ring), 7.14 (t, 2H, 4'-ring), 7.83 (br, 2H, 6'-ring).

In a parellel series of experiments, 9-benzyl-6-chloropurine (36), prepared from hypoxanthine, was converted to the oxime ether 79 (61.6%) and the hydrazine[54] 81 (86.6%) by procedures outlined for the preparation of 74 and 76 from 4 (*vide supra*). Similarly 7-benzyl-6-chloropurine (37) and 9-tetrahydropyranyl-6-chloropurine (41) were also transformed, respectively, to oxime ethers 80 (60%) and 82 (76%). The structural assignment for these compounds is supported by spectral and analytical data. Thermolysis of the oxime ethers 79 and 80 either neat or in solvents such as o-dichlorobenzene gave complex mixtures. The oxime ether 82 on neat thermolysis gave a 20% yield of 9-tetrahydropyranyl hypoxanthine (83) (CHART C.28 and CHART C.29).

79: mp. 170°C

ir : ν_{max}(KBr) cm^{-1}: 1590, 1570 (C=C, C=N), 1060 (C-O).

nmr: $\delta(CDCl_3)$ 60 MHz: 2.2 (d, 2H, $-N=C(C\underline{H}_3)_2$), 5.4 (s, 2H, $-C\underline{H}_2-\emptyset$), 7.3 (s, 5H, phenyl), 7.9 (s, 1H, 8'-purine ring), 8.6 (s, 1H, 2'-purine ring).

80: mp. 155°C

ir : ν_{max}(KBr) cm^{-1}: 1610, 1545 (C=C, C=N), 1040 (C-O).

nmr: $\delta(CDCl_3)$ 60 MHz: 1.9, 2.1 (s, s, 3H, 3H, $-N=C(C\underline{H}_3)_2$), 5.6 (d, 2H, $-C\underline{H}_2-\emptyset$), 7.1 (m, 5H, phenyl), 8.0 (s, 1H, 8'-purine ring), 8.7 (s, 1H, 2'-purine ring).

CHART.C.28

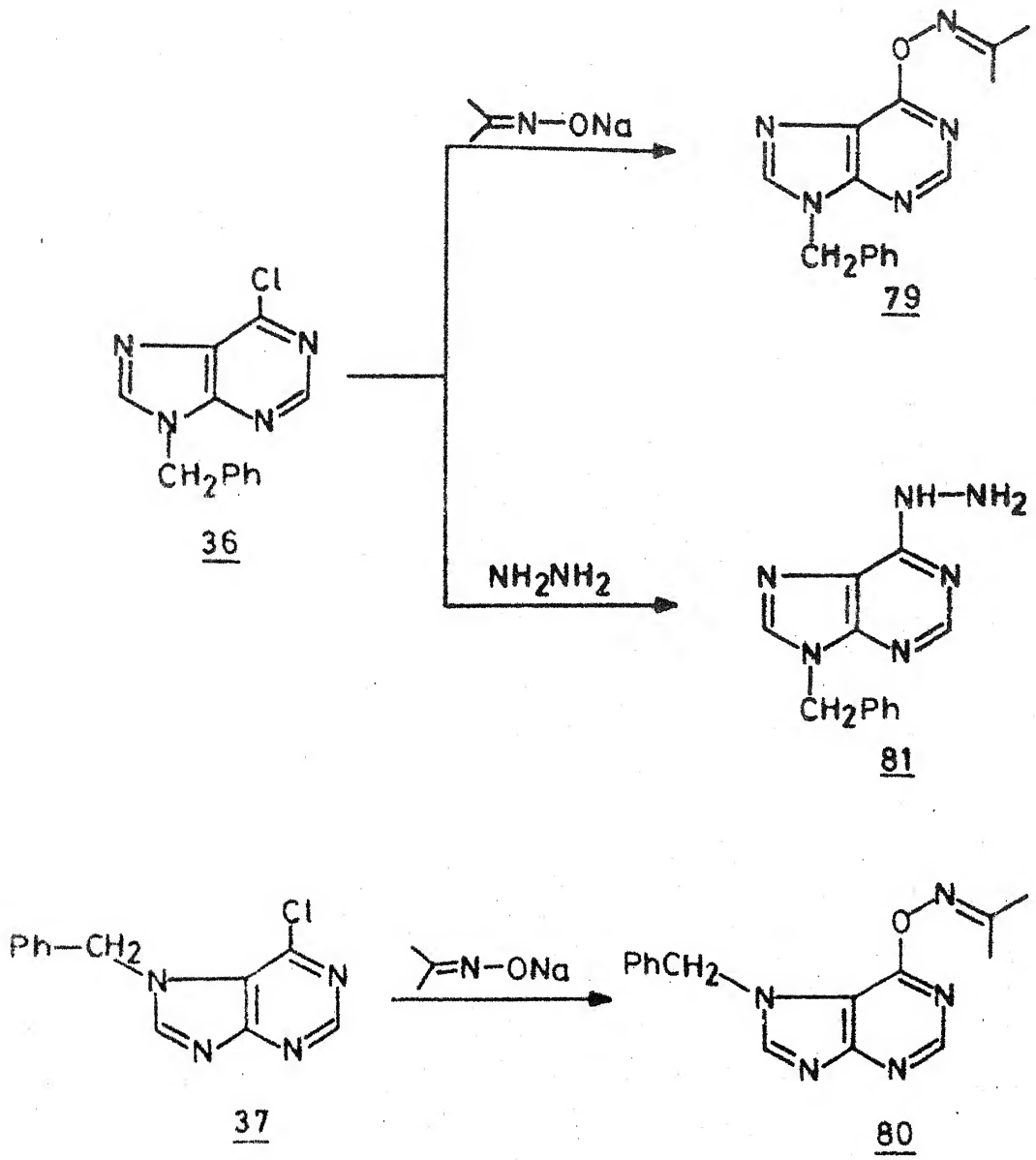

Cl
N
N
N
N
CH2Ph
36
=N—ONa
NH2NH2
O
N
CH2Ph
79
NH—NH2
81
Ph—CH2
37
PhCH2
80

CHART . C .29

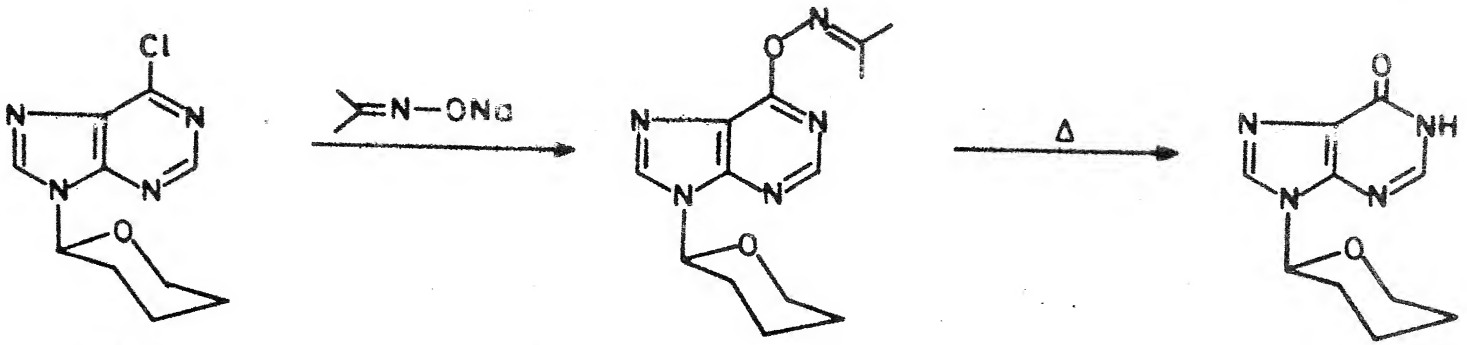
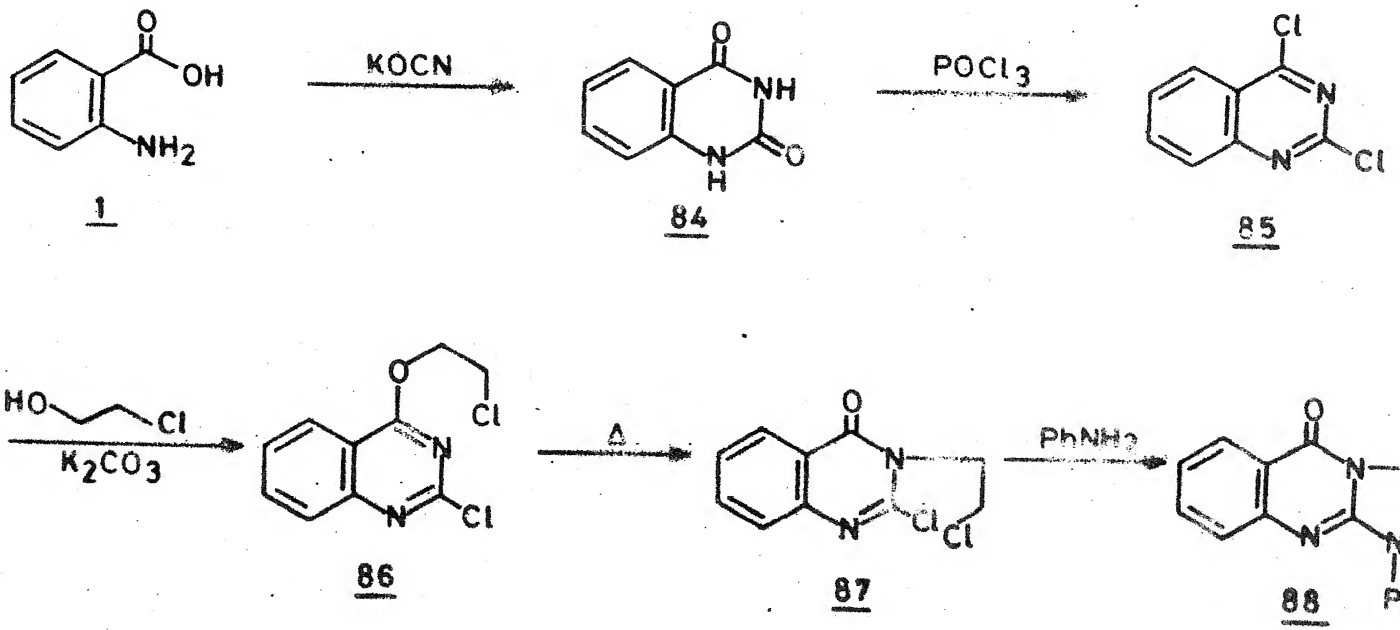


CHART . C .30



81: mp. 209°C

82: mp. 135°C

ir : ν_{max}(KBr) cm^{-1}: 2950, 2810 (saturated CH), 1590, 1570, 1540 (C=C, C=N), 1050 (C-O).

nmr: $\delta(CDCl_3)$ 60 MHz: 1.9 (m, 6H, THP-ring), 2.1, 2.2 (s, s, 3H, 3H, $-N=C(C\underline{H}_3)_2$), 3.9 (m, 2H, $O-C\underline{H}_2-$), 5.6 (m, 1H, $-N-C\underline{H}-O-$), 8.0 (s, 1H, 8'-purine ring), 8.5 (s, 1H, 2'-purine ring).

83: mp. 198-200°C

Mass:m/e: 220 (M^+)

ir : ν_{max}(KBr) cm^{-1}: 3400 (NH), 1690 (amide carbonyl).

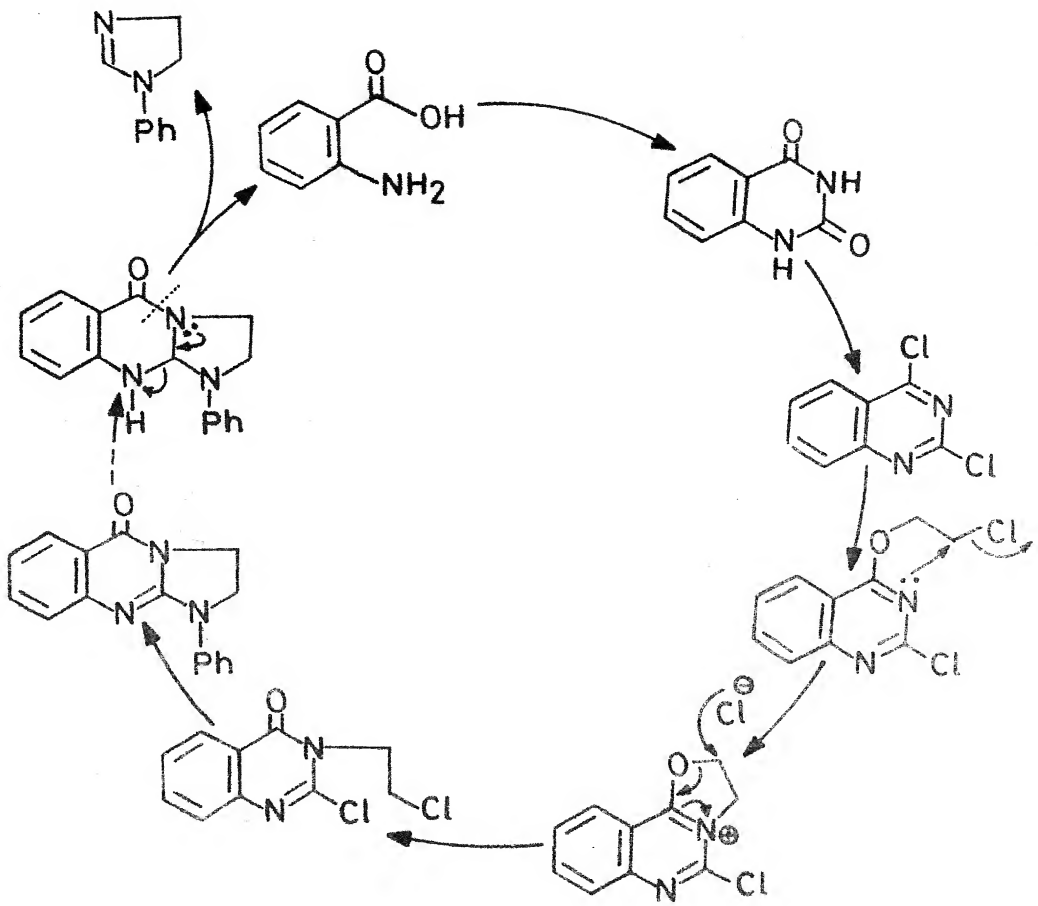
nmr: δ(DMSO-d_6) 200 MHz: 1.4-1.9 (m, 6H, THP ring), 3.75 (m, 2H, $-O-C\underline{H}_2-$), 5.6 (m, 1H, $-N-C\underline{H}-O-$), 8.1 (s, 1H, 8'-purine ring), 8.3 (s, 1H, 2'-purine ring).

With the realisation of difficulties associated with the formation of tricyclic systems that are of relevance to the chemical simulation of the cycle, it was considered appropriate to effect the synthesis of such suitably substituted compounds and then examine the possibilities of their transformations to the daughter products and the parent templates. Interestingly,

a number of natural products are known, where a five membered ring is attached to a parent quinazoline system[75]. It was felt that the known tricyclic system 88 would be an ideal choice for changes along the cycle, since, it could not only lead to the daughter product, N-phenylimidazoline but also regenerate the parent model template, that is the focus of the present work, namely, anthranilic acid. Indeed, the synthesis of the tricyclic system 88 is so fortuitously chartered that the further transformations of 88 to N-phenylimidazoline and anthranilic acid would constitute yet another strategic approach to the chemical sumulation of the ATP-Imidazole Cycle (CHART C.X). It may be noted that in this approach, the 3-Nitrogen and the 2-carbon of the potential imidazole molecule are simultaneously introduced as the quinazoline-2,3-positions. The oxidation state of the resulring 1,2,3,4-tetrahydro-2,4-dioxoquinazoline is higher, thus, warranting a reduction at a subsequent stage ! (CHART C.X).

Reaction of anthranilic acid (1) with freshy prepared KCNO[76] gave in 85% yields 1,2,3,4-tetrahydro-2,4-dioxoquinazoline[77] (84) which on treatment with $POCl_3$ gave, as reported, 2,4-dichloroquinazoline[78] (85) (89%). Compound 85 underwent with ethylene chlorohydrin in presence of K_2CO_3 specific ether formation leading to 2-chloro-4-(2'-chloroethyl) ether[79] 86 (84%). Mere distillation of 86 led to, in 80% yields, 3-(2'-chloroethyl)-2-chloro-3,4-dihydro-4-oxoquinazoline[79] 87. The 86 → 87 thermal transformation is noteworthy. In many ways it resembles the

CHART C.X


N
N
Ph
O
OH
NH2
O
NH
N
H
O
Cl
N
Cl
O
N
Cl
Cl
Cl
O
N
Cl
O
N
H
Ph
O
N
N
Ph
O
N
N
Cl
Cl
O
N
Cl

novel [3,3] changes of the quinazoline system reported in the present work, since this change also encompasses the specific N^3-alkylation with concomitant generation of the 4-oxoquinazoline system. However, the mechanism of this change is quite different from that related to the [3,3] shift. In all probability, the first step is the formation of a quinazolinium chloride arising from intramolecular halogen displacement. The generated halide ion regiospecifically attacks the carbon adjacent to the oxygen atom leading to 87 (CHART C.X). This change could have synthetic potential since the intermediate quinazolinium ion could be intercepted with more effective nucleophiles, thus opening up a method for the synthesis of diverse N^3-substituted 3,4-dihydro-4-oxoquinazolines. The reaction of 87 with aniline gave rise to the key tricyclic system [80] 88 in 81.2% yields. The 87 → 88 change almost certainly involves the initial addition of aniline to the 1-2 bond of 87, displacement of the chloride and cyclisation of the resulting 2-anilinoquinazolone. The structural assignments for product 84, 85, 86, 87 and 88 are in good agreement with that reported (CHART C.30).

84: mp. > 360°C

85: mp. 118°C

86: mp. 103°C

ir : ν_{max}(KBr) cm^{-1}: 1610, 1570, 1550 (C=C, C=N), 1100 (C-O).

nmr: $\delta(CDCl_3)$ 60 MHz: 3.85 (t, 2H, -O-$\underline{CH_2}$-), 4.8 (t, 2H, -$\underline{CH_2}$-Cl), 7.2-7.85 (m, 3H, 6',7',8'-quinazoline ring), 8.1 (m, 1H, 5'-quinazoline ring).

87: mp. 92°C

ir : ν_{max}(KBr) cm^{-1}: 1680 (amide carbonyl), 1580, 1560 (C=C, C=N).

nmr: $\delta(CDCl_3)$ 60 MHz: 3.8(t, 2H, -N-$\underline{CH_2}$-), 4.6 (t, 2H, -$\underline{CH_2}$-Cl), 7.2-7.9 (m, 3H, 6',7',8'-quinazoline ring), 8.1 (m, 1H, 5'-quinazoline ring).

88: mp. 165°C

ir : ν_{max}(KBr) cm^{-1}: 1670 (amide carbonyl), 1620, 1580, 1550 (C=C, C=N).

nmr: $\delta(CDCl_3)$ 60 MHz: 3.85 (m, 4H, -N-$\underline{CH_2}$-$\underline{CH_2}$-N-), 7.2-8.3 (m, 9H, aromatic).

It could be readily seen that compound 88 could be placed on the cycle, provided that the 1-2 bond on the quinazoline moiety, can be reduced. Further endeavours were totally directed to achieving this objective. In the event, however, the reduction of this bond was found to be particularly difficult, no

doubt, because of its highly nucleophilic nature. Conditions that are normally employed for the reduction of diverse types of C=N bonds did not succeed. Thus attempted reduction of 88 with B_2H_6-THF, B_2H_6-BF_3-THF, $NaBH_4$, catalytic hydrogenation under different conditions and using different catalysts, the reduction of the acetyl salt, all gave the starting material. The trimethyl silyl salt of 88 namely 92 was readily prepared and treatment of this with $NaBH_4$ led to the isolation of 88 in excellent yields. Atleast in this case it was demonstrated that the additional nitrogen that is present in the 2-position of the quinazoline moiety is making a substantial contribution to the recalcitrant behaviour of 88 towards acceptance of electrons. Thus, the trimethylsilyl salt 51 prepared from 3-allyl-3,4-dihydro-4-oxoquinazoline (6) underwent smooth sodiumborohydride reduction leading to 3-allyl-1,2,3,4-tetrahydro-4-oxoquinazoline (91) (CHART C.32). The structural assignment for 92 and 91 are supported by sprectral data.

92: mp. 253°C

ir : ν_{max}(KBr) cm^{-1}: 2300-2700 (br)(salt).

91: bp. 200°C/0.2 mm

ir : ν_{max}(neat) cm^{-1}: 3300 (NH), 1670 (amide carbonyl), 1640, 1610 (C=C).

CHART.C.31

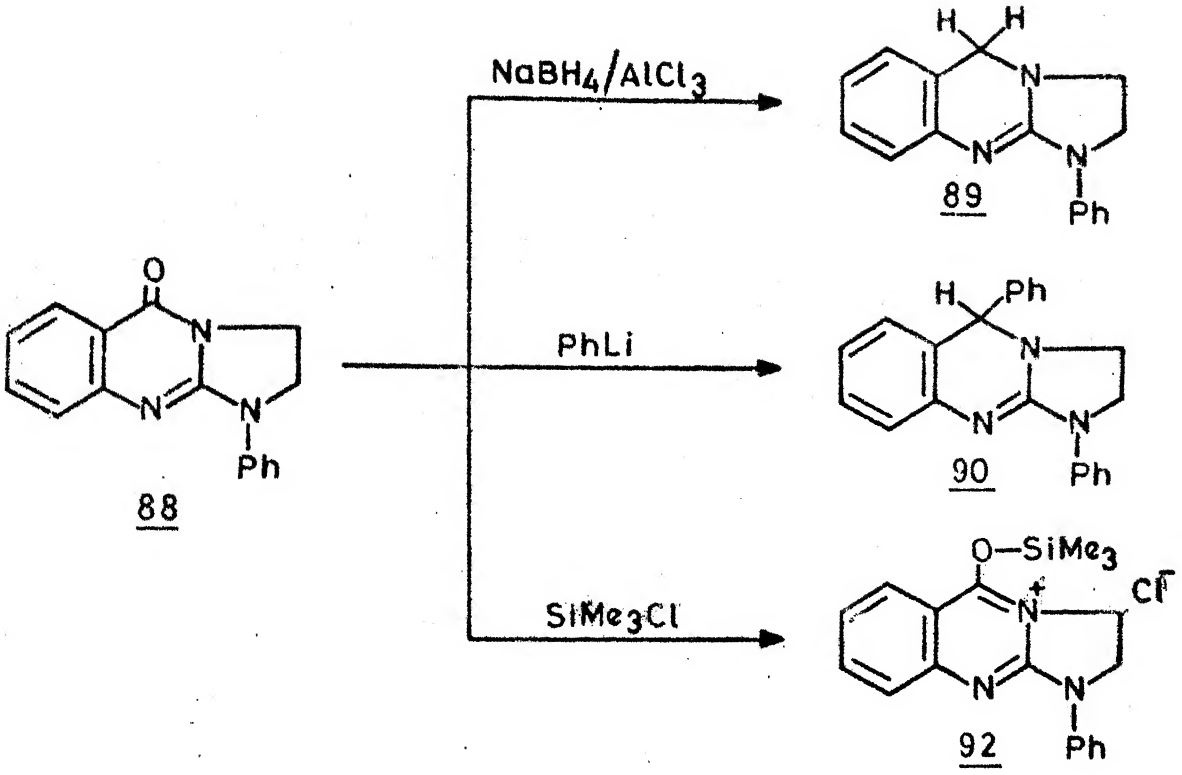
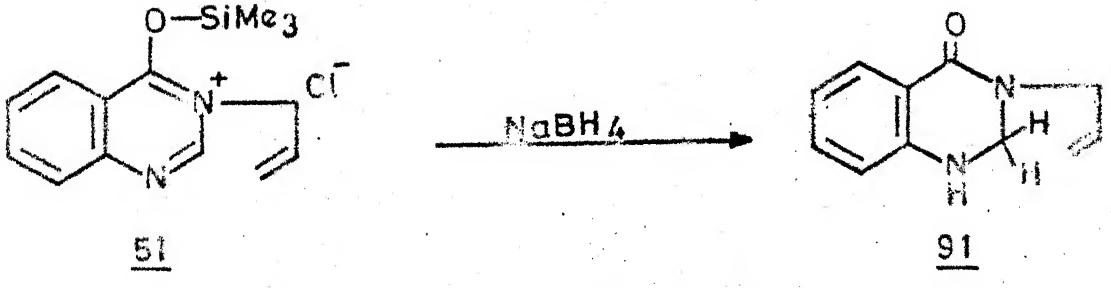


CHART.C.32



nmr: $\delta(CDCl_3)$ 60 MHz: 4.1, 4.5 (m, m, 2H, 2H, -N-$\underline{CH_2}$-CH, N-$\underline{CH_2}$-N), 5.2 (m, 2H, -CH=$\underline{CH_2}$), 5.9 (m, 2H, -$\underline{CH}$=CH_2), 6.5-8.3 (m, 4H, aromatic).

Eventually, it was possible to reduce 88 under quite forcing conditions via reduction of the $AlCl_3$ complex with $NaBH_4$ in diglyme at 85°C. Unfortunately, the 1-2 bond survived this harsh treatment and the 4-oxo unit completely removed, leading to the isolation of interesting tricyclic system 89 in 83% yields[81]. The structural assignment for 89 is supported by spectral data (CHART C.31).

89: mp. 188-90°C

Mass: m/e: 249(M^+)

ir : ν_{max}(KBr) cm^{-1}: 1620, 1580, 1560 (C=C, C=N).

nmr: $\delta(CDCl_3)$ 60 MHz: 3.2 (m, 2H, -$\underline{CH_2}$-CH_2-N-Ø), 3.7 (m, 2H, -CH_2-$\underline{CH_2}$-N-Ø), 4.2 (s, 2H, 4'-quinazoline ring), 6.7-7.4 (m, 3H, 6',7',8'-quinazoline ring), 7.75 (dd, 1H, 5'-quinazoline ring).

In another approach, compound 88 was reacted with PhLi with the expectation that, as in earlier cases, addition to the

quinazoline 1-2 bond could take place leading to the removal of the unwanted 1-2 π-bond. Such a system could be processed to the daughter 1-2 diphenyl imidazoline and the model template anthranilic acid. Surprisingly, the reaction when carried out gave a 88% yield of 90 amounting to the replacement of the 4-oxo system with a phenyl group. The structural assignment for 90 is supported by spectral data (CHART C.31). The formation of 90, can be rationalised, on the basis of the further transformations of the adduct of PhLi to the 4-oxo grouping of the quinazoline moiety of 88. This intermediate could lead to a very highly stabilished 4-phenyl quinazolinium unit, which via acceptance of electrons from the reagent could lead to the observed product.

90: mp. 193-5°C

ir : ν_{max}(KBr) cm^{-1}: 3030 (aromatic CH), 1630, 1570, 1520 (C=C).

nmr: $\delta(CDCl_3 + DMSO\text{-}d_6)$ 90 MHz: 3.3 (m, 2H, 3'-ring), 3.75 (m, 2H, 2'-ring), 6.5-8.0 (m, 15H, 5'-ring, aromatic).

Finally, endeavours to cleave the tricyclic system 88 with a variety of nucleophiles such as aqueous NaOH, NaOMe-MeOH and NaCN-aq. MeOH did not succeed.

The present work describes endeavours relating to the chemical simulation of the salient features of the ATP-Imidazole Cycle, incorporating experimentation in three distinct phases that encompasses the total operation, namely,

1. the preparation of specifically and appropriately N^3-substituted 3,4-dihydro-4-oxoquinazolines and the preparation of protected specifically and appropriately N^1-substituted purines.

2. the cyclisation of a variety of specifically N^3-substituted quinazolines to tricyclic systems that are related to the cycle.

3. selective cleavage of N^3-substituted 3,4-dihydro-4-oxoquinazolines.

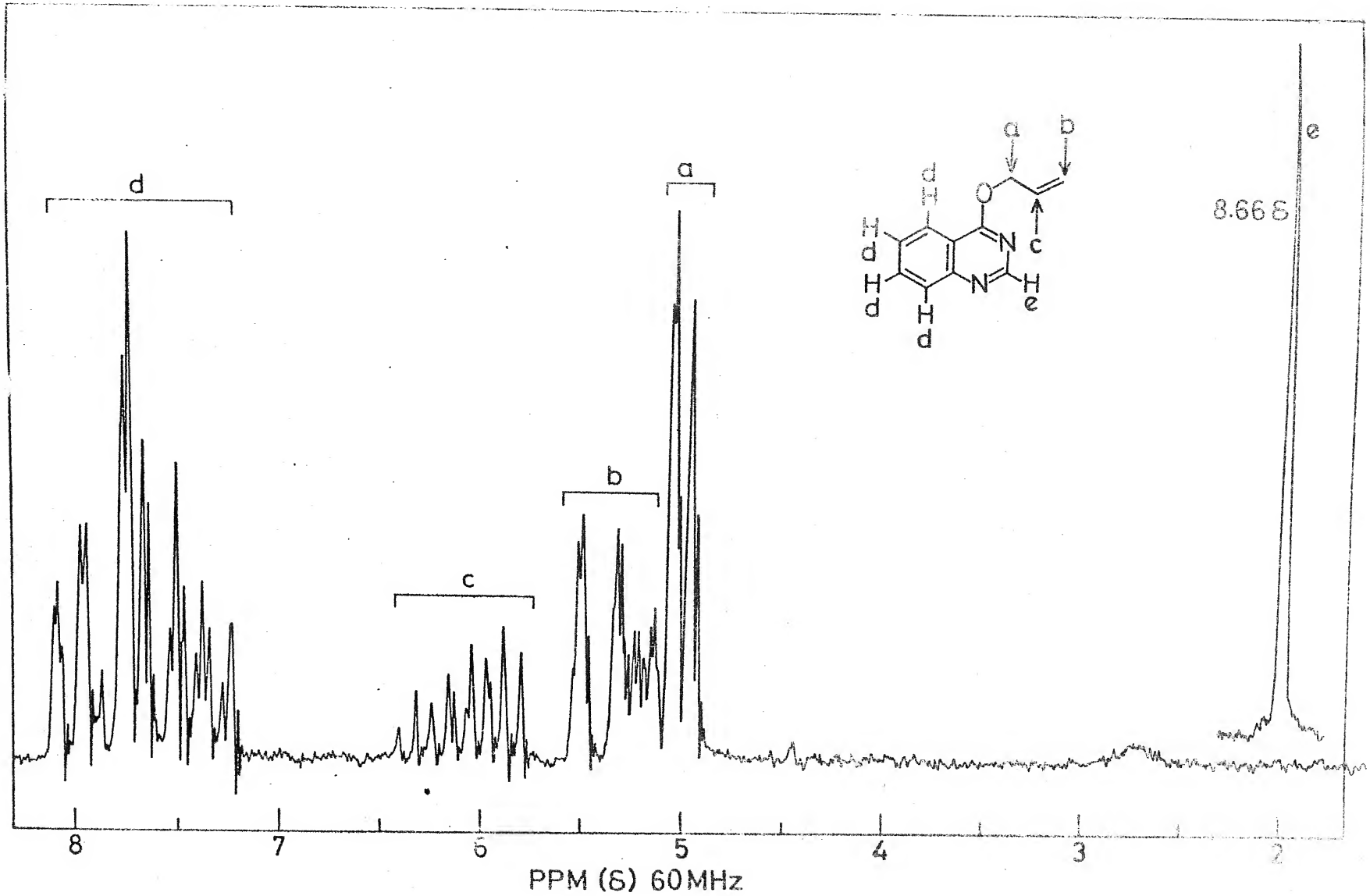
The objectives with reference to the first phase has been, by and large, accomplished. Methods and methodologies have been developed, for the preparation of a variety of, often novel, quinazolines and purines.

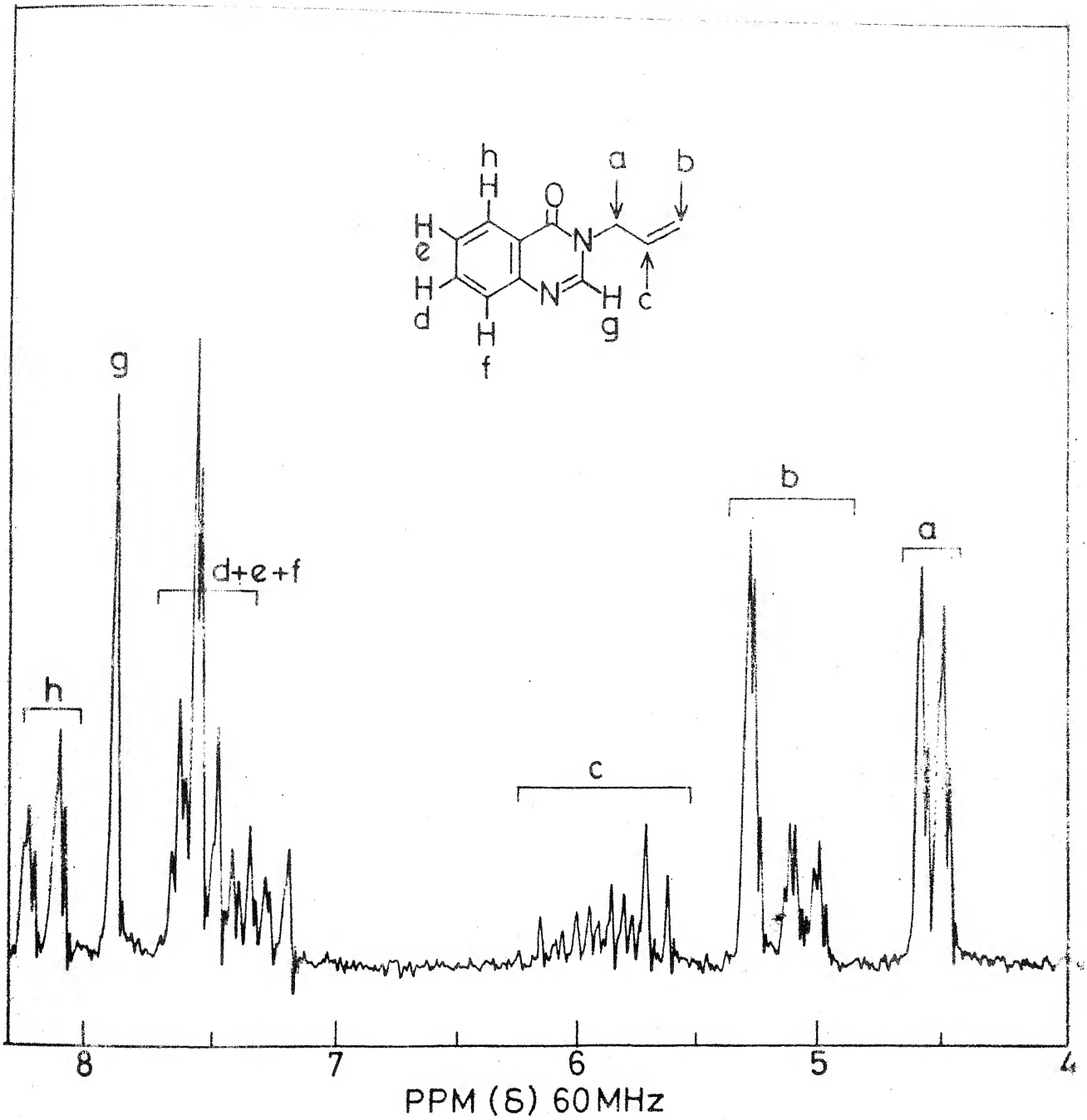
The cyclisation efforts pertaining to the second stage, although could not be solved, have brought out, above all, quite forcefully, the highly electrophilic nature of the 1-2 bond of N^3-substituted 3,4-dihydro-4-oxoquinazolines. Success here proved elusive, because either the tricyclic systems produced were so fragile as to make further studies infructuous, as in the case of 9, 11 and 45 or such systems existing in equilibrium were

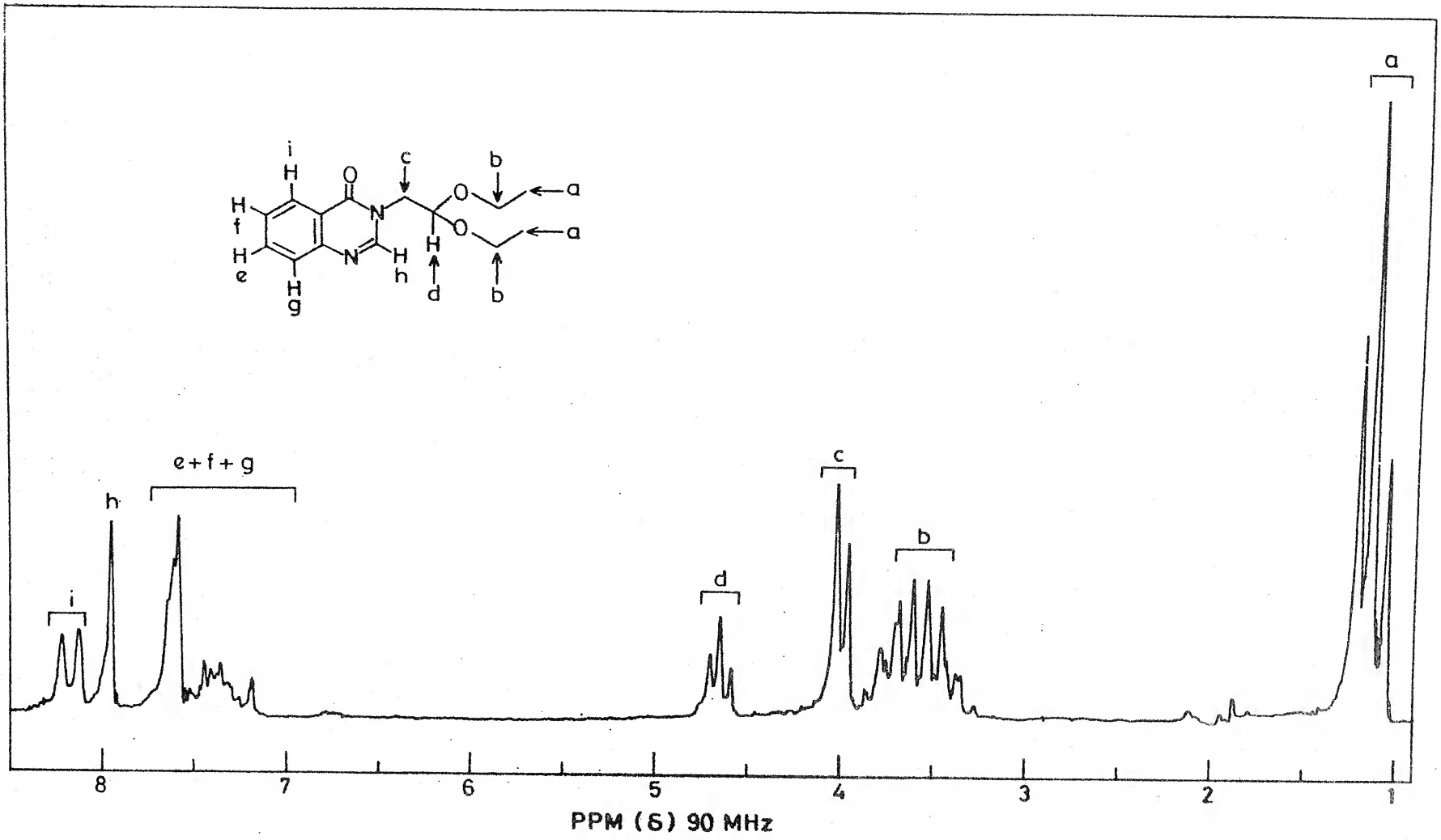
removed *via* irreversible addition to the 2-position by external nucleophiles. Thus, the conditions for the successful cyclisation is delicately poised and the present work has helped to define factors, where such a cyclisation can occur. The cyclisation endeavours have brought to light several facets of new chemistry relating to the reaction of N^3-substituted 3,4-dihydro-4-oxoquinazolines with organometallic reagents that function either as a nucleophile or as a base or both.

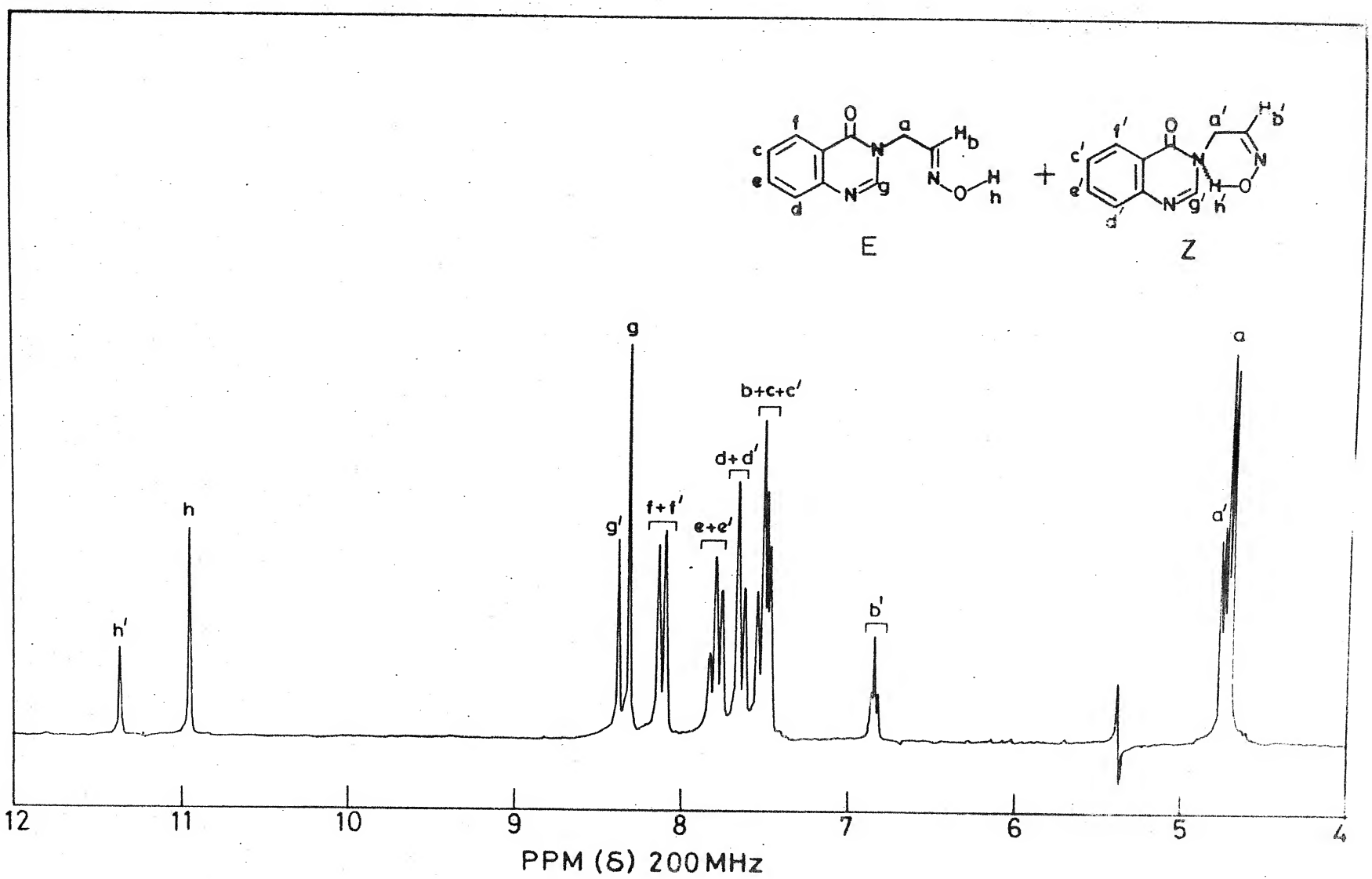
Attempts to hydrolytically cleave N^3-substituted 3,4-dihydro-4-oxoquinazolines to products useful to the cycle did not succeed. It appears that the scission of the 4-oxo grouping would be more attractive, since, addition to the reactive 1-2 bond is likely to result in the loss of the 2-carbon that is pivotal to the formation of the daughter product. Thus, if the addition to the 1-2 bond is discouraged *via* substitution at the 2-position, the cleavage of the 4-oxo grouping may result. A very promising lead in this direction is the alkylation of 9-benzyladenine with ethylenebromohydrin leading to 71. This compound, possessing a reactive imino grouping, can be fragmented to a nitrile by appropriate 1'-substitution.

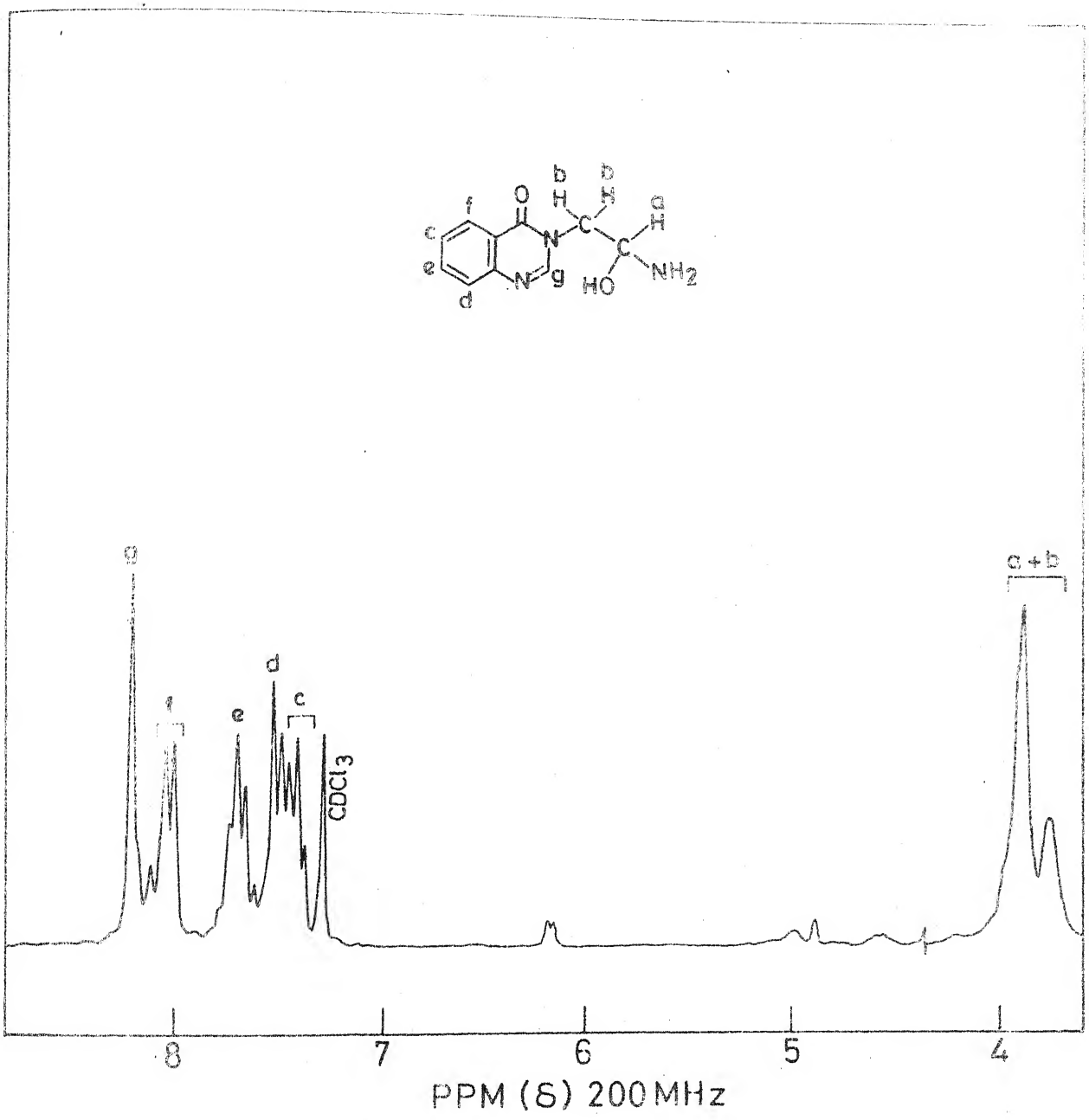
It may be concluded that the present work has enabled the construction of a broad based basic strategic framework that would eventually pave the way for the realisation of the solution to the problem.

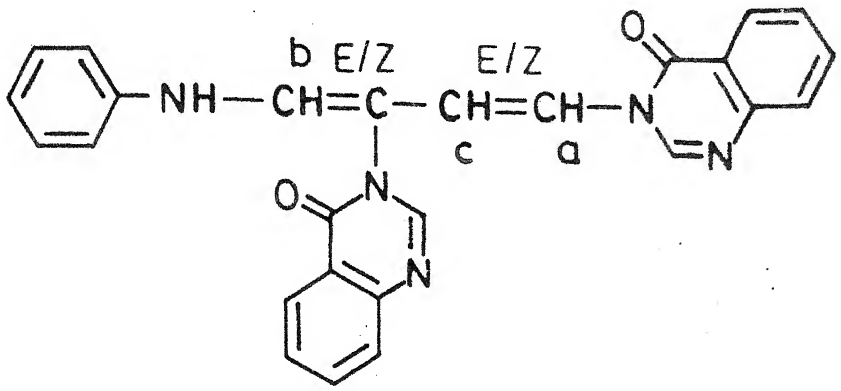

d
a
b
c
e
8.66 δ
a
b
c
d
d
d
d
e
N
N
O
8
7
6
5
4
3
2
PPM (δ) 60 MHz

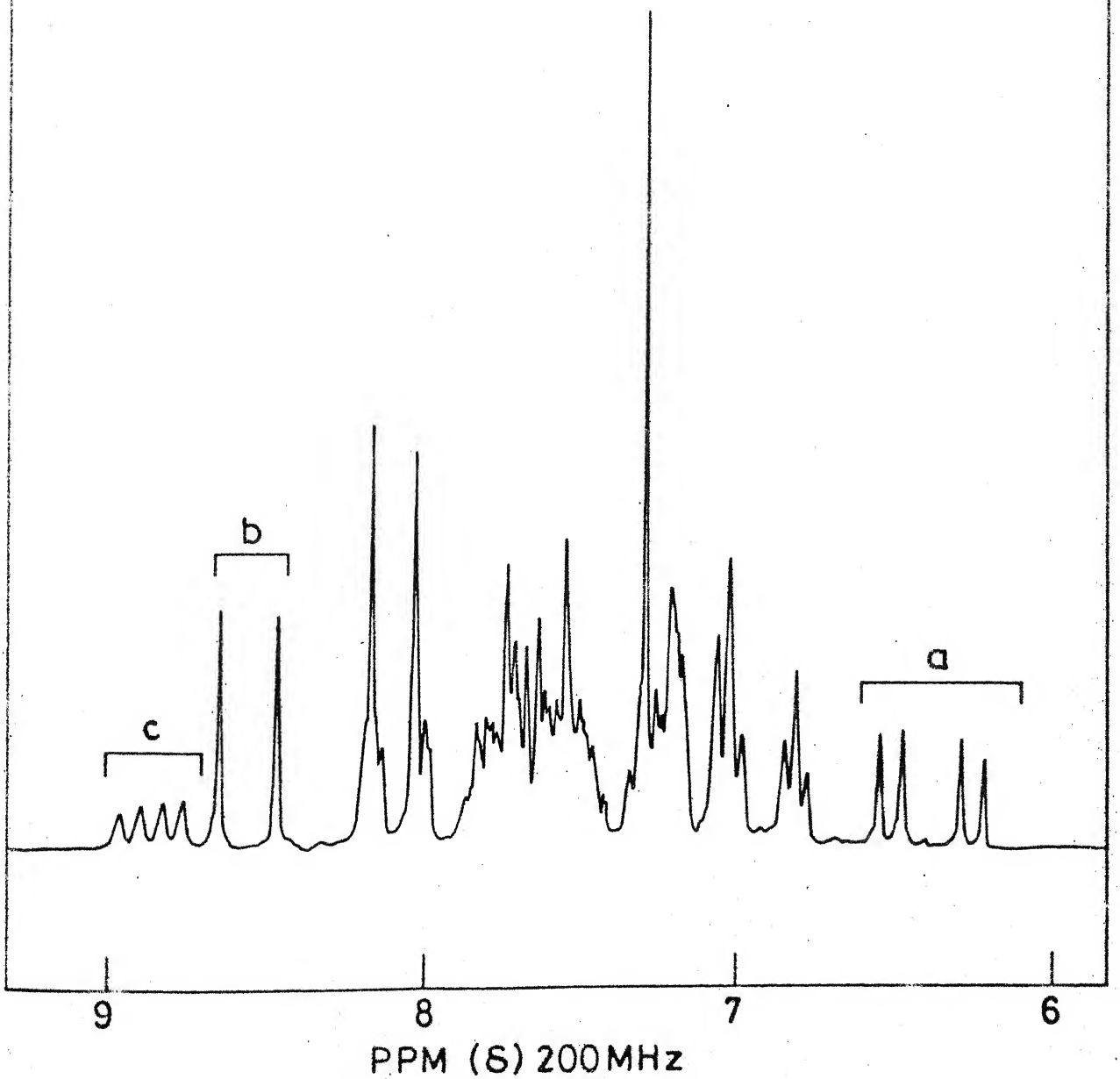

h
H
a
b
O
H
e
N
H
d
N
H
c
H
f
g
g
b
a
d+e+f
h
c
8
7
6
5
4
PPM (δ) 60 MHz

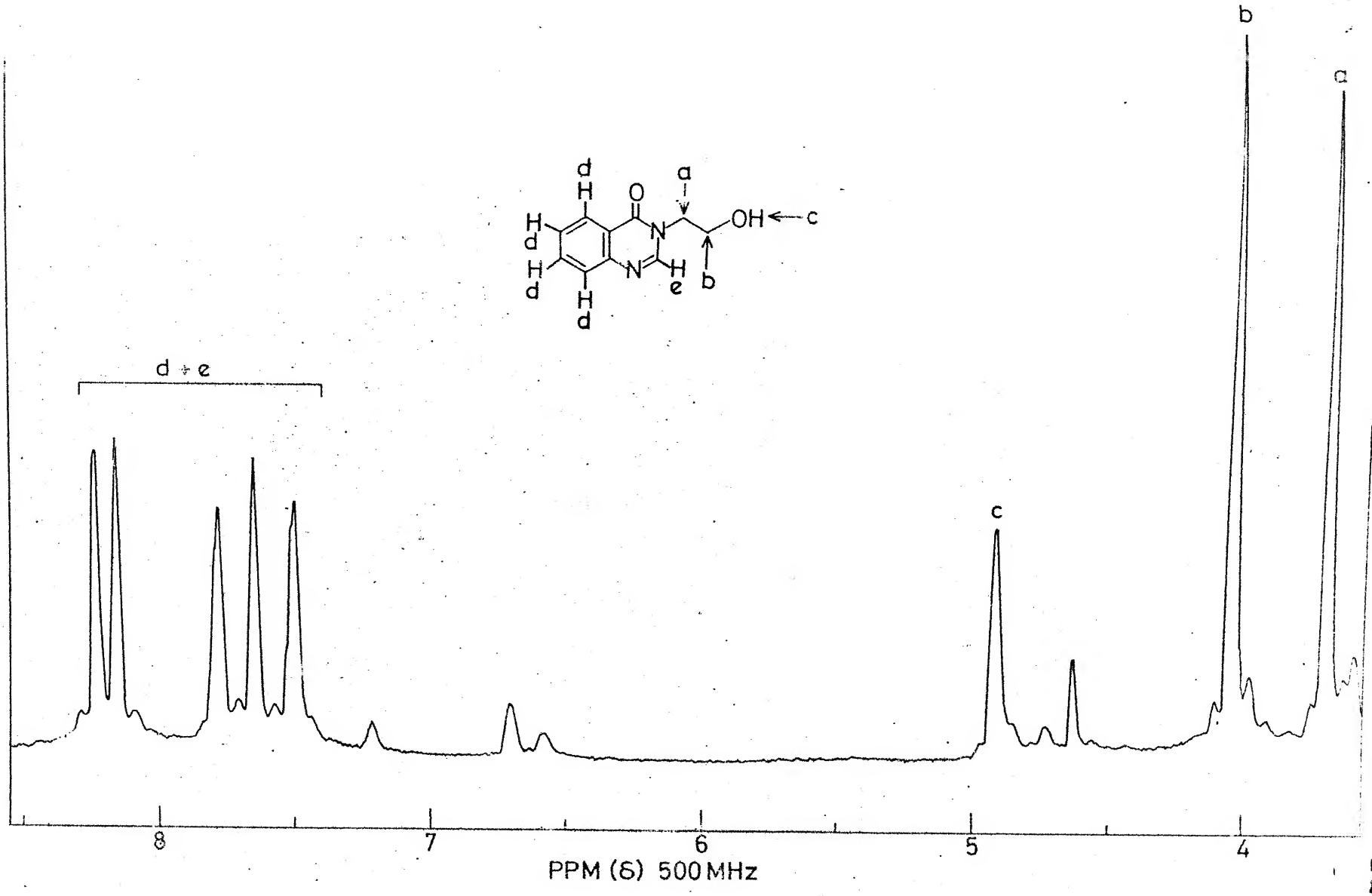

i
H
O
c
b
a
H
f
N
O
a
H
e
N
H
h
H
g
H
d
b
a
e+f+g
h
c
i
d
b
8
7
6
5
4
3
2
1
PPM (δ) 90 MHz

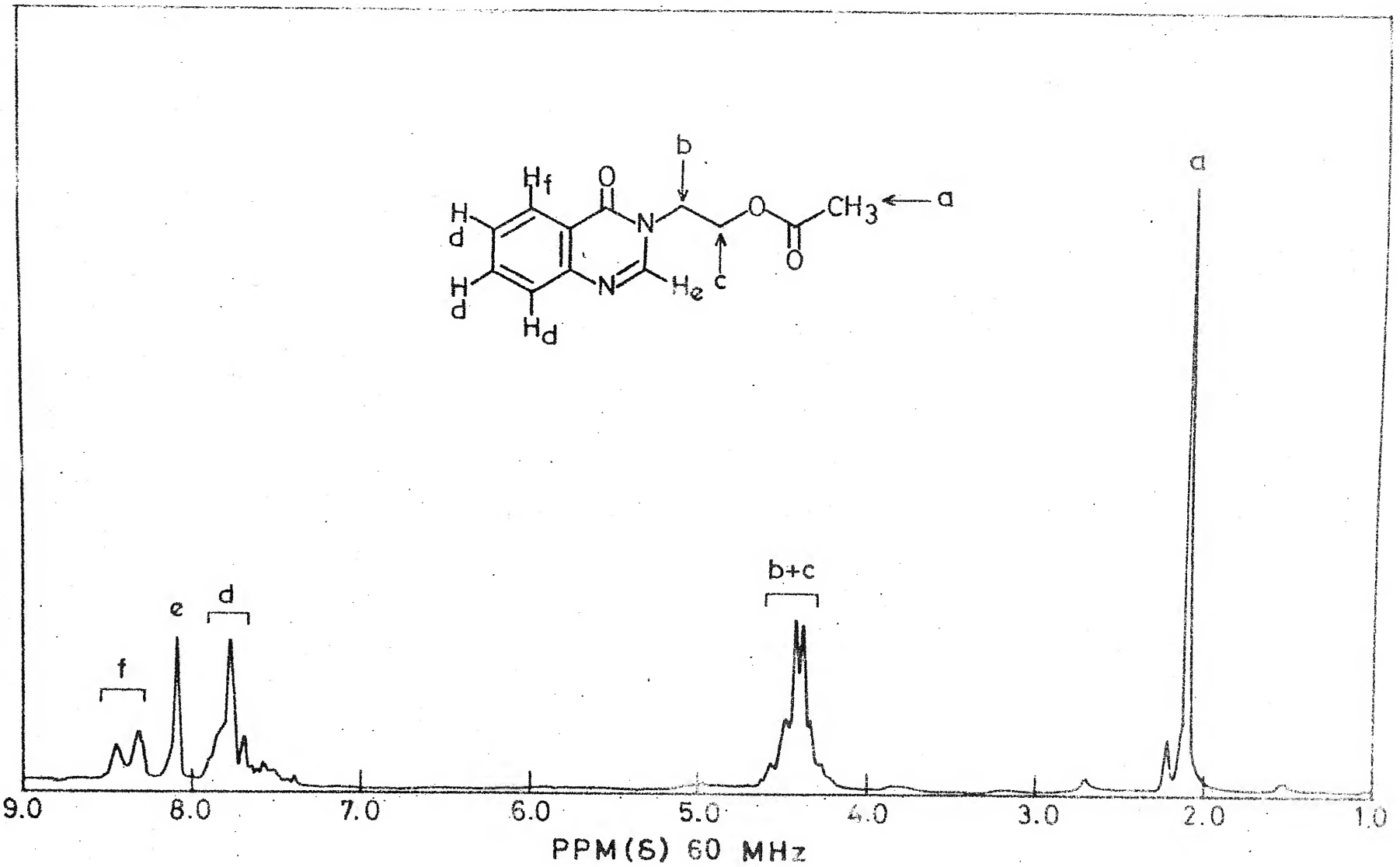

E
Z
h'
h
g'
g
f+f'
e+e'
d+d'
b+c+c'
b'
a'
a
12
11
10
9
8
7
6
5
4
PPM (δ) 200 MHz

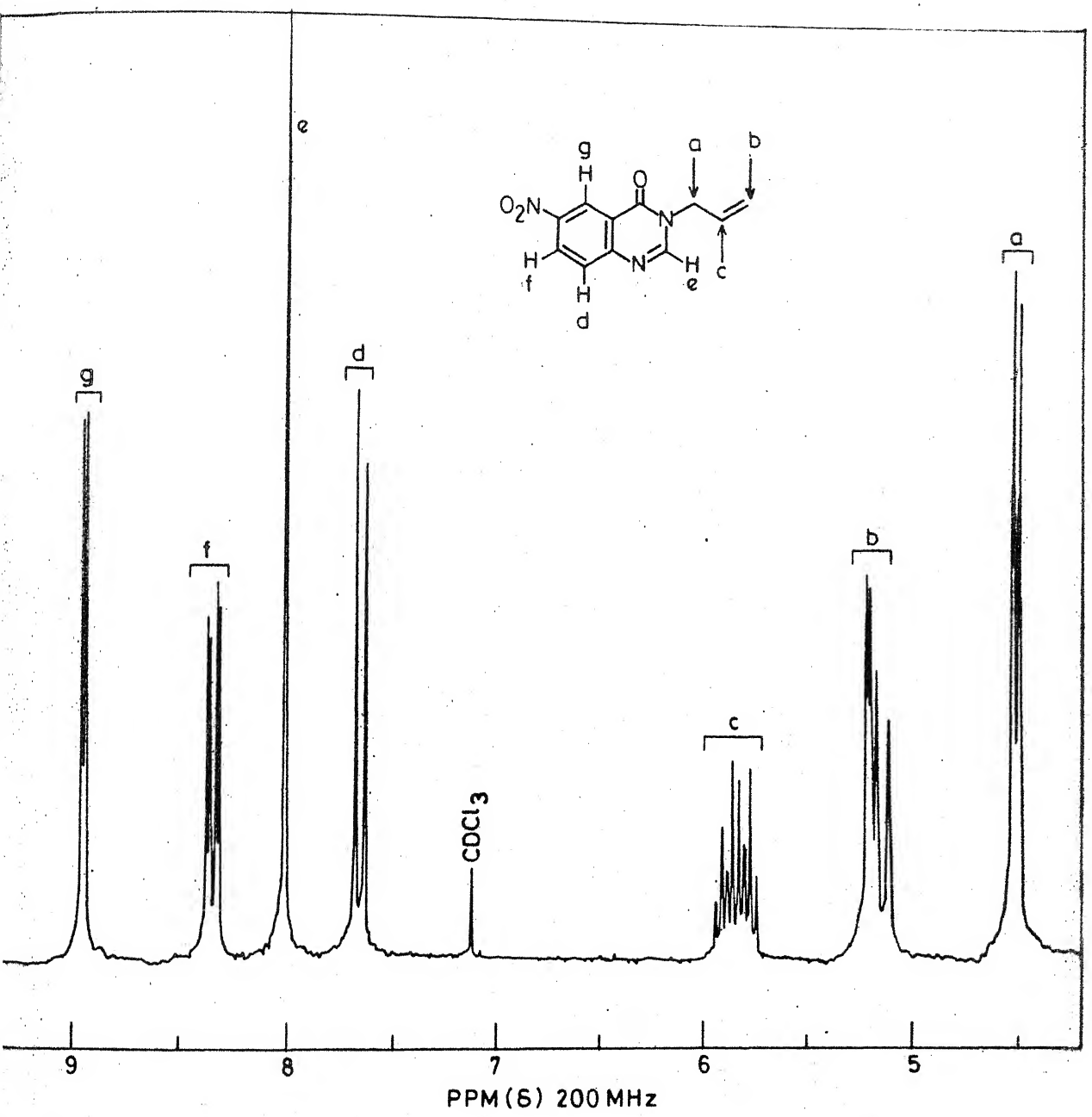

O
b
H
b
H
f
c
N
C
a
H
e
N
g
C
HO
NH2
d
g
f
e
d
c
CDCl3
c + b
8
7
6
5
4
PPM (δ) 200 MHz

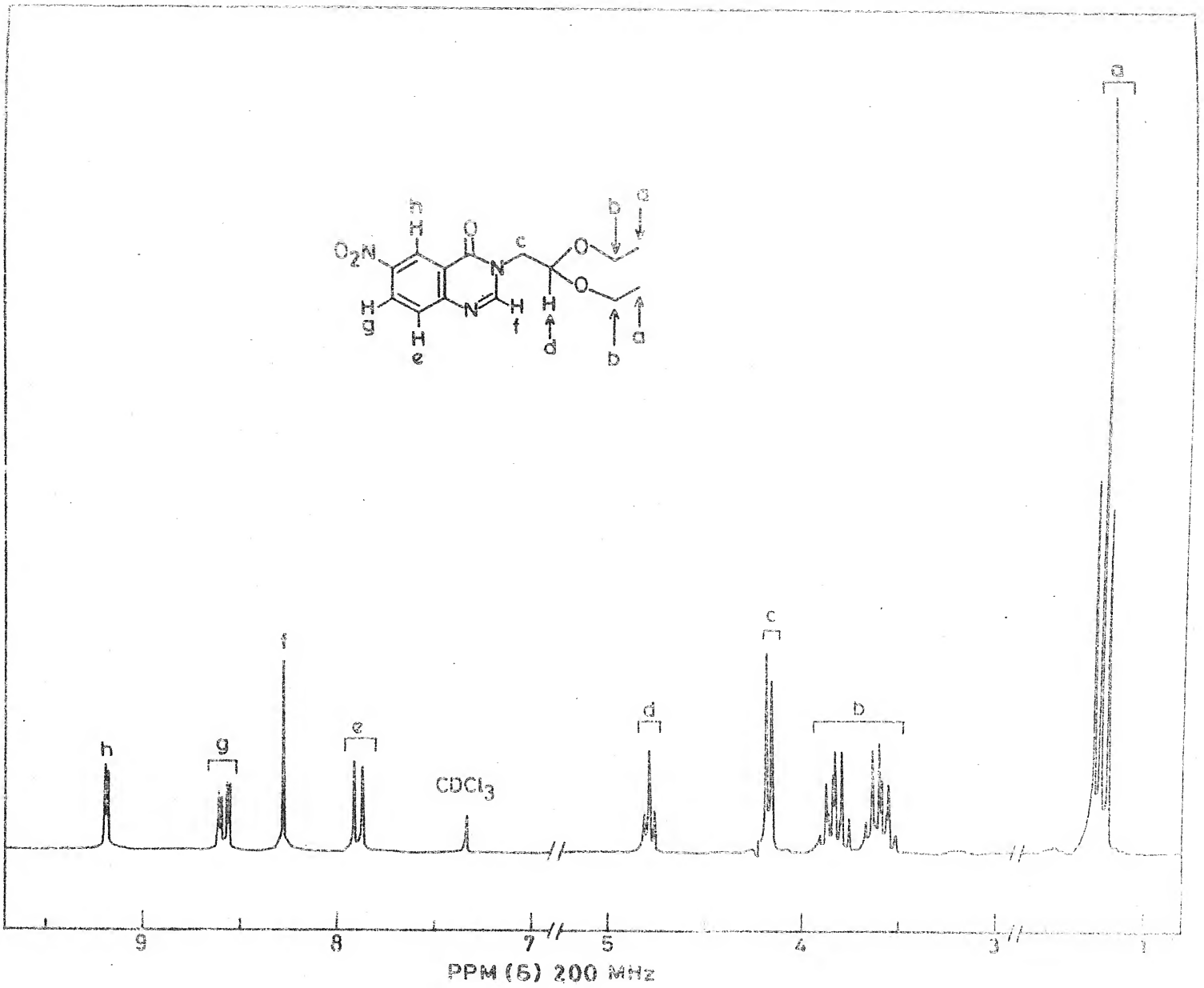

b E/Z
E/Z
NH
CH=C
CH=CH
c
a
O
N
N
O
N
N

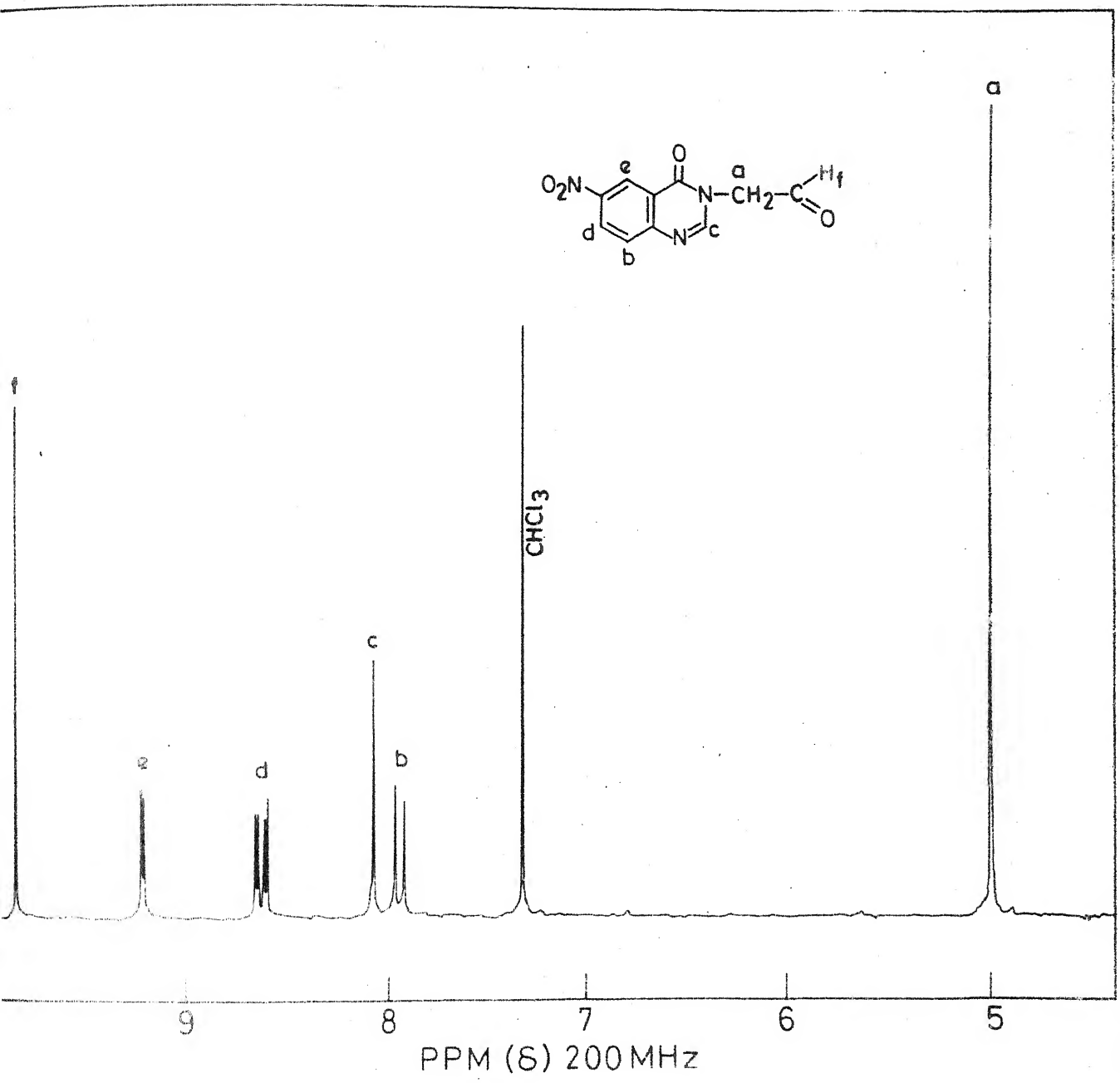

b
c
a
9
8
7
6
PPM (δ) 200MHz

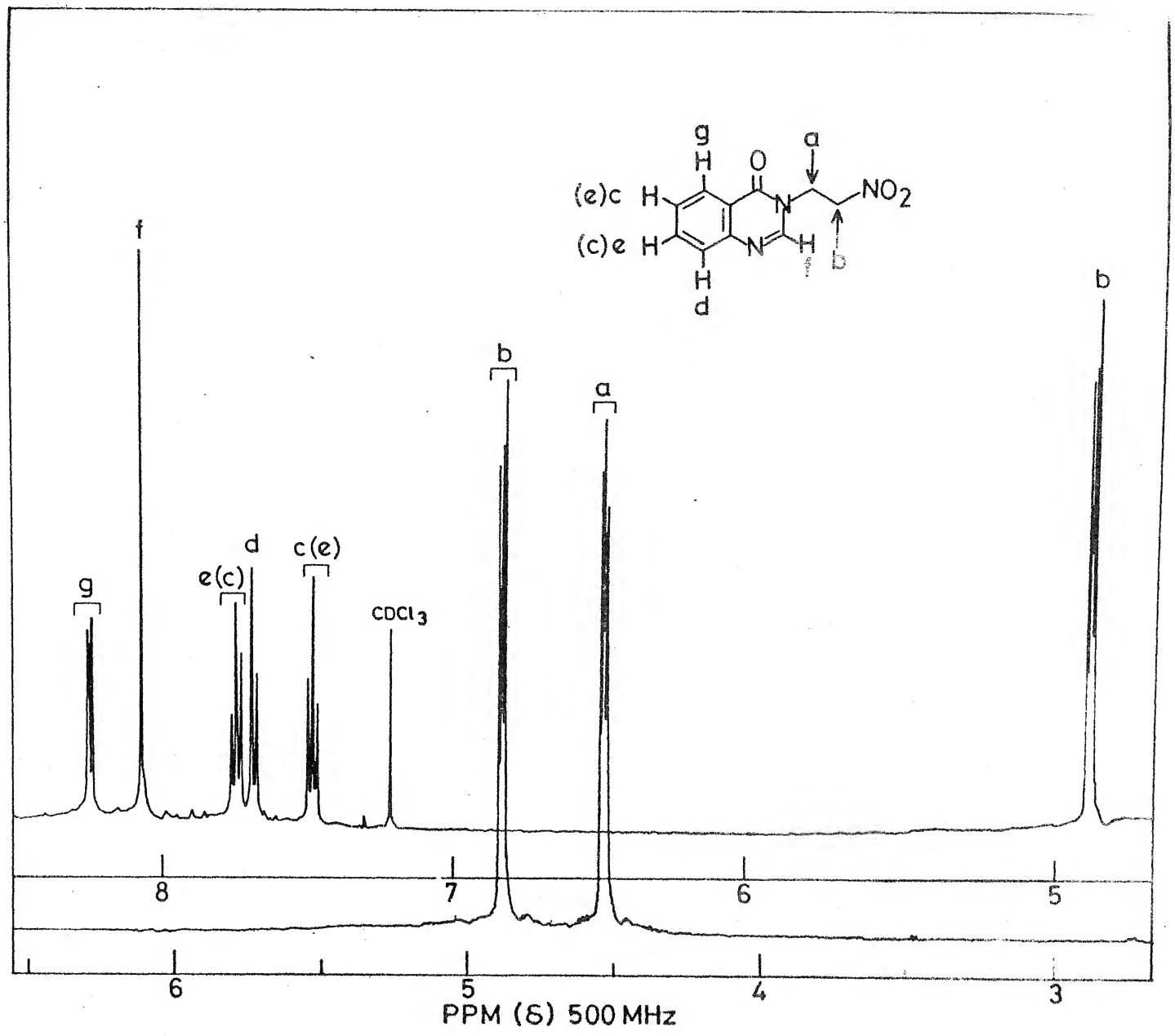

b
a
d
H
O
a
OH
c
H
d
H
d
N
N
H
e
b
H
d
d + e
c
8
7
6
5
4
PPM (δ) 500 MHz

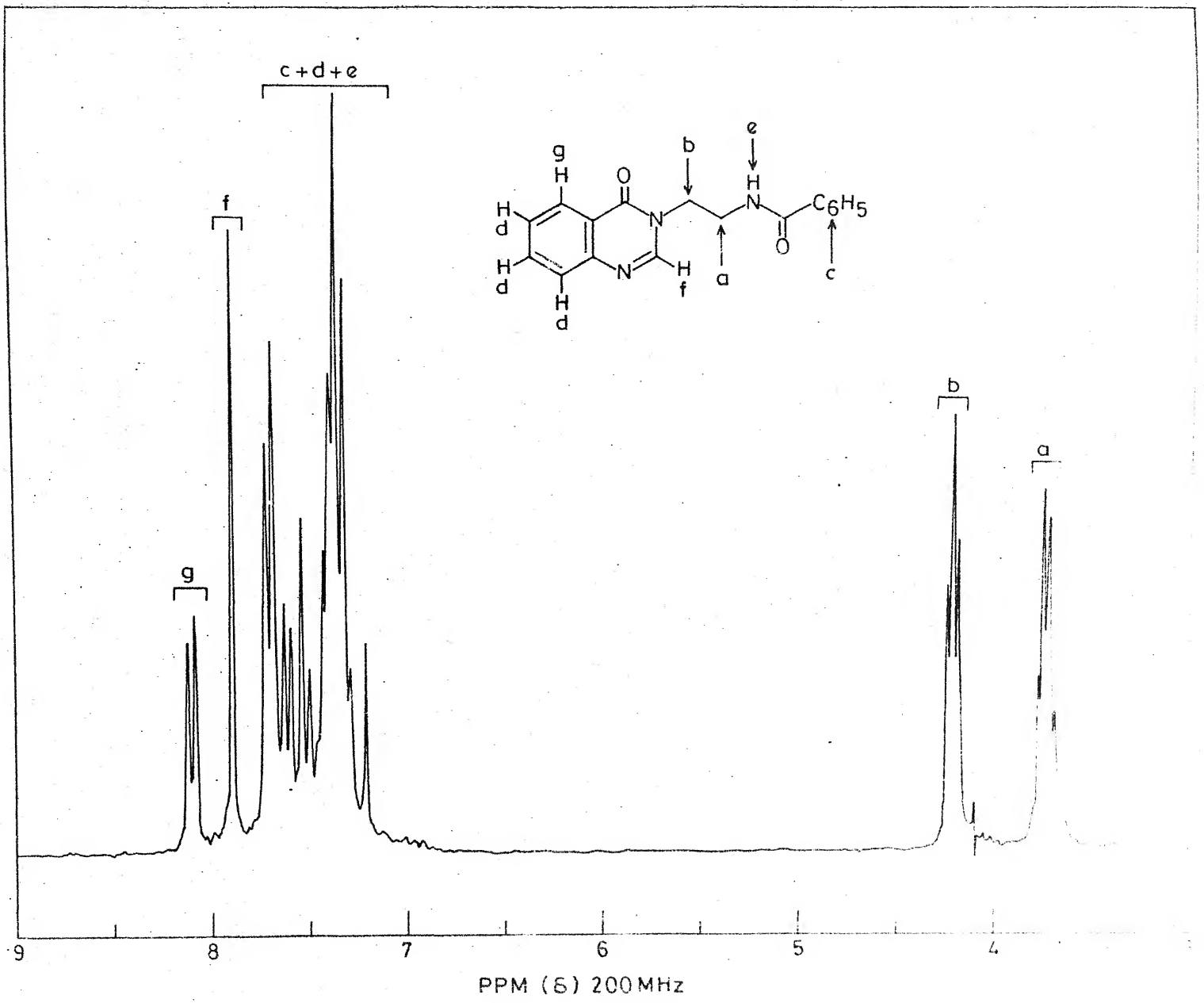

b
a
H_f
O
H
d
H
d
N
N
H_e
c
O
O
CH_3
a
H_d
f
e
d
b+c
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM(δ) 60 MHz

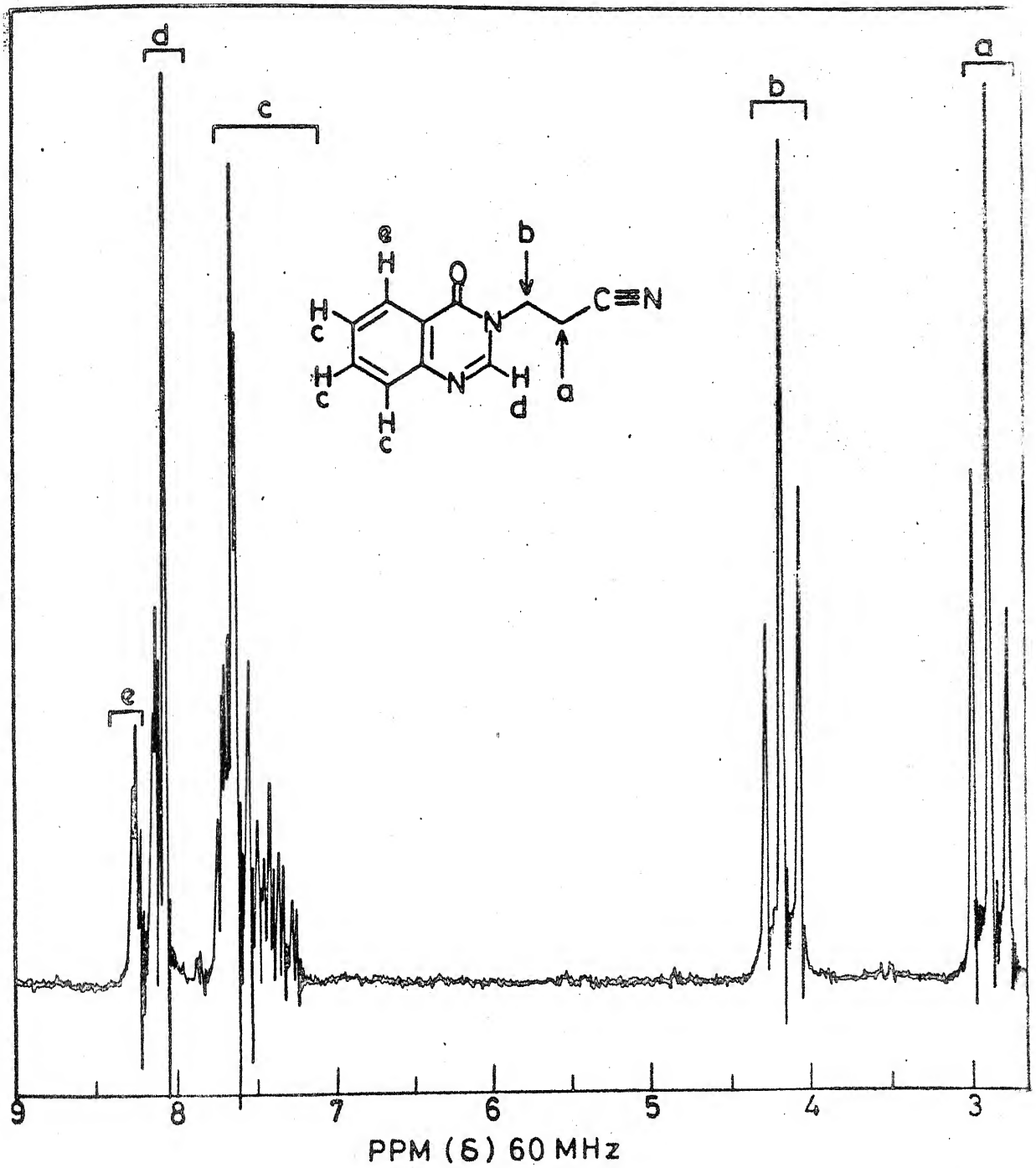

e
g
a
b
O_2N
O
N
H
H
H
H
f
e
c
d
g
f
d
b
a
c
$CDCl_3$
9
8
7
6
5
PPM (δ) 200 MHz

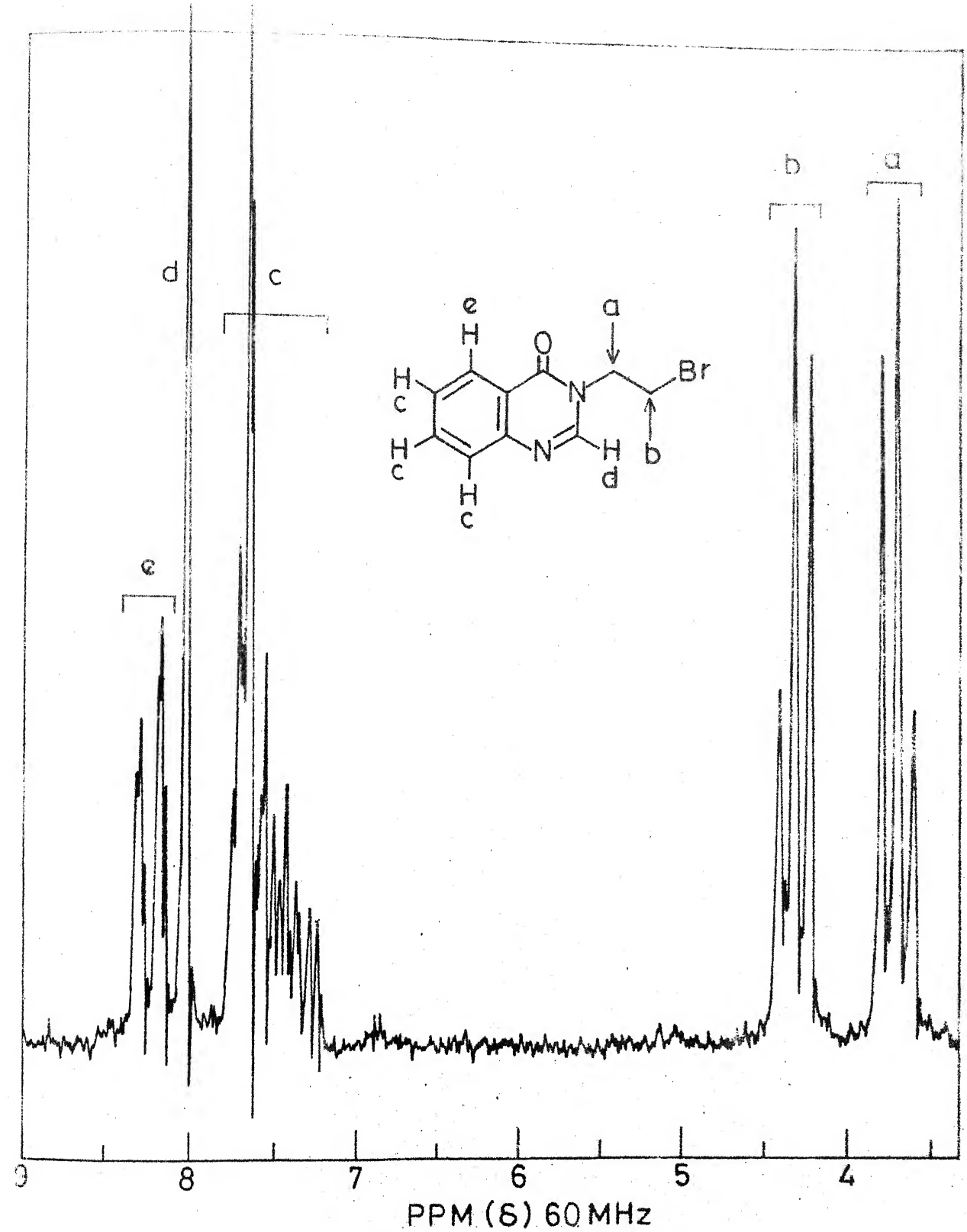

h
g
f
e
CDCl3
d
c
b
a
9
8
7
5
4
3
PPM (δ) 200 MHz

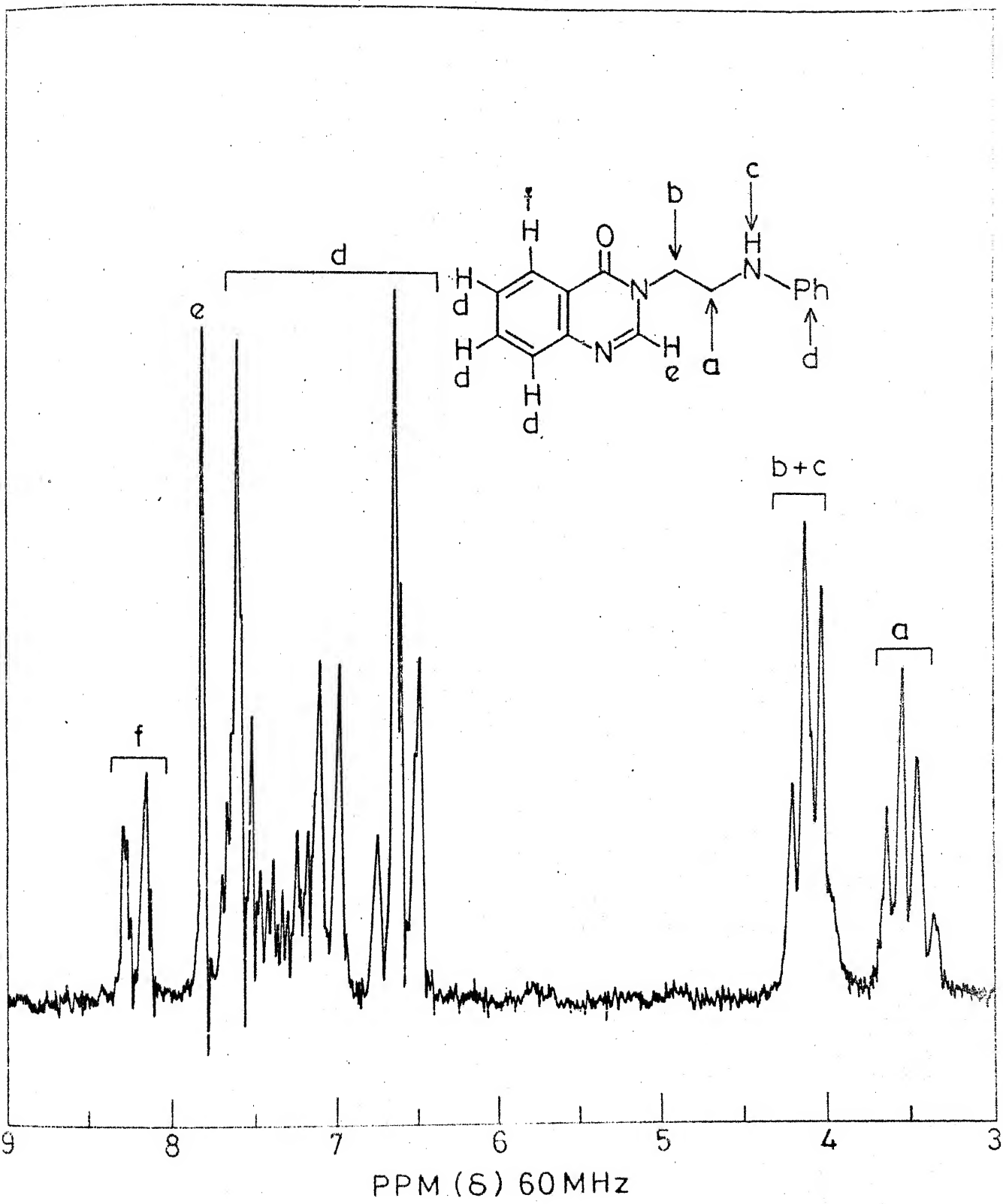

a
f
e
d
c
b
CHCl3
9
8
7
6
5
PPM (δ) 200 MHz

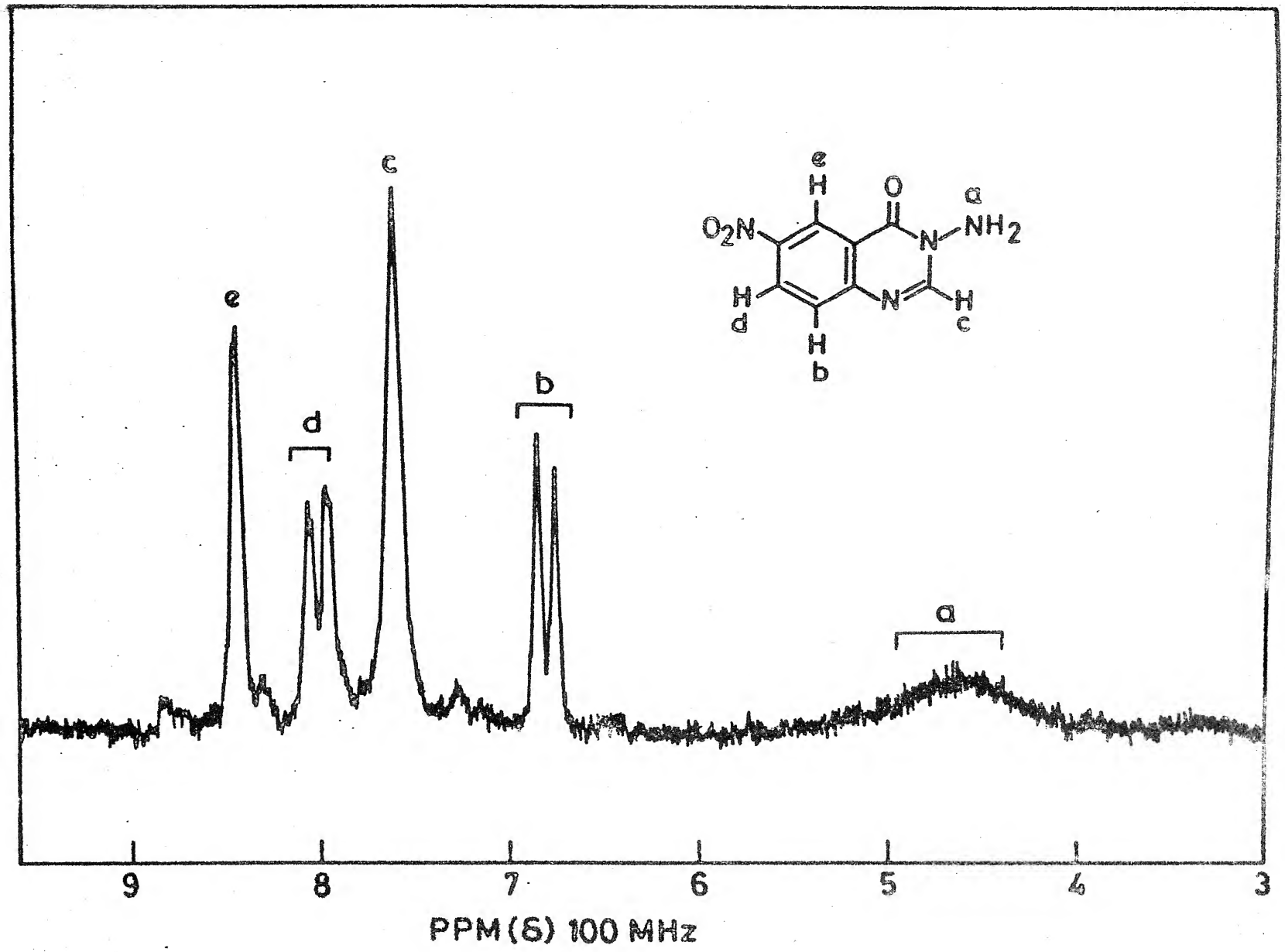

g
H
O
a
(e)c H
NO2
(c)e H
N
H
f
b
H
d
f
b
b
a
g
e(c)
d
c(e)
CDCl3
b
8
7
6
5
6
5
4
3
PPM (δ) 500 MHz

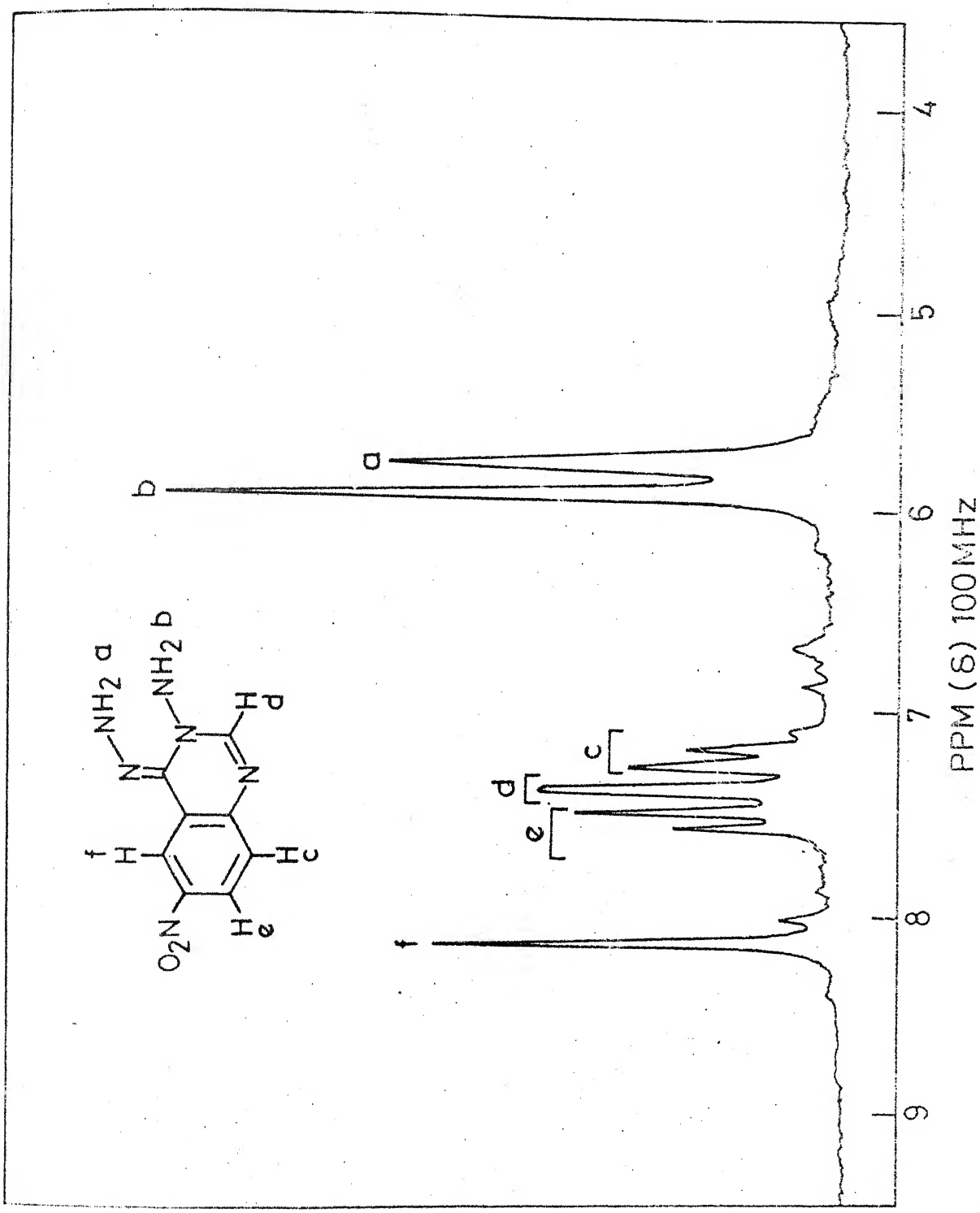

c+d+e
f
g
b
a
g
H
H
d
H
d
H
d
O
N
N
H
f
b
e
H
N
O
C_6H_5
a
c
9
8
7
6
5
4
PPM (δ) 200 MHz

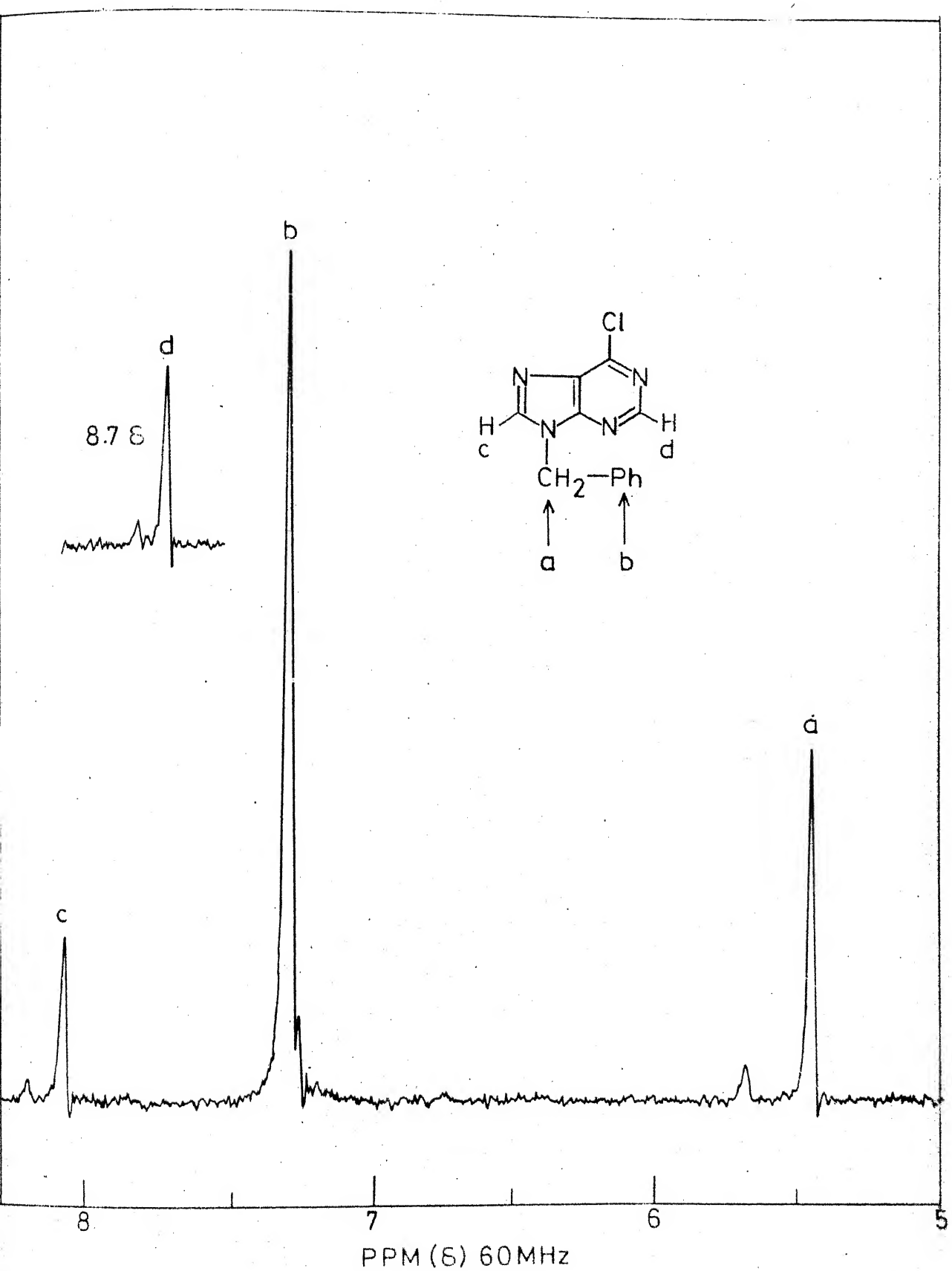

d
c
b
a
e
e
H
O
b
C≡N
H
c
N
H
c
N
H
d
a
H
c
9
8
7
6
5
4
3
PPM (δ) 60 MHz

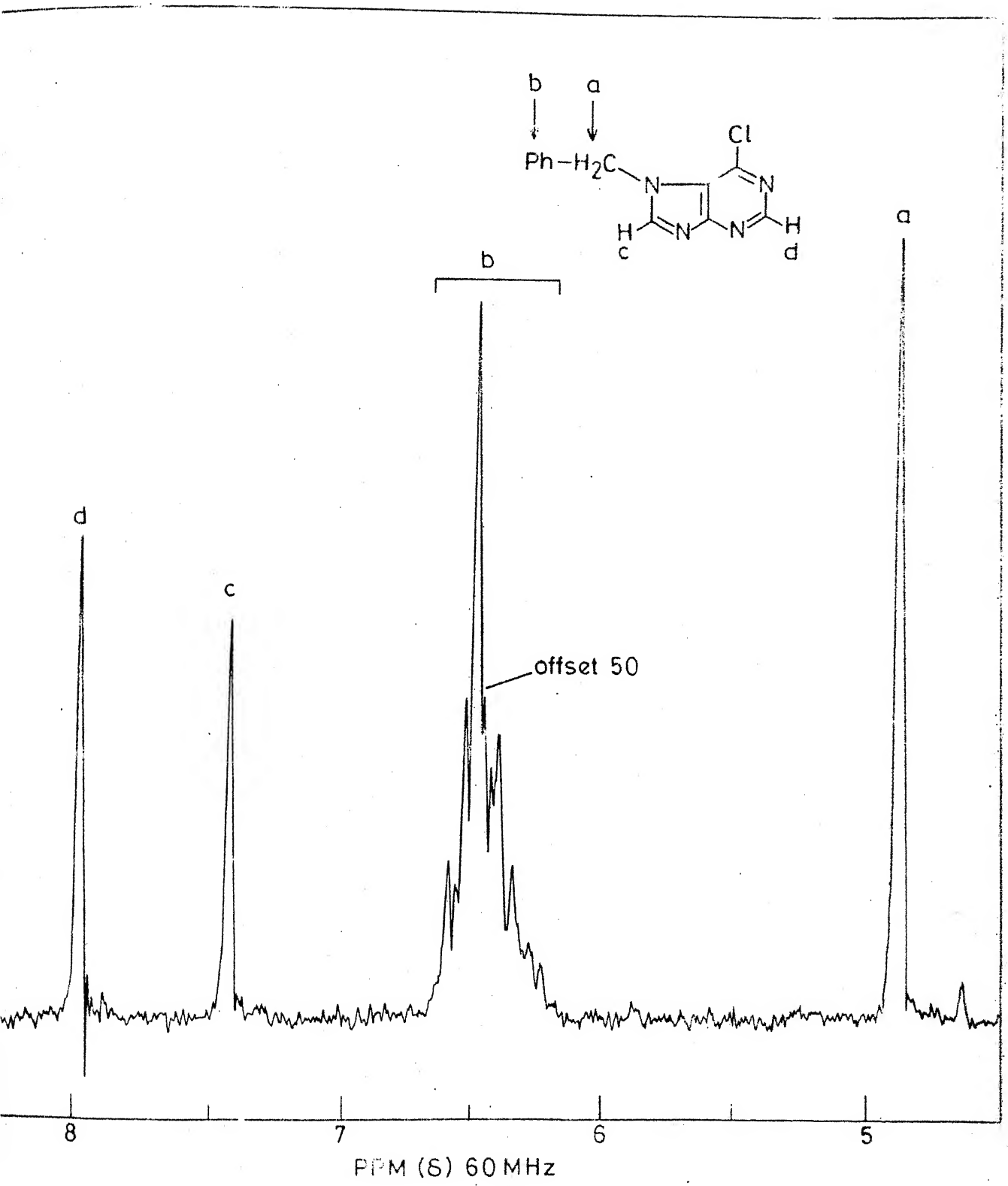

b
a
d
c
e
a
H
O
Br
H
c
N
H
c
N
H
d
b
H
c
e
8
7
6
5
4
PPM (δ) 60 MHz

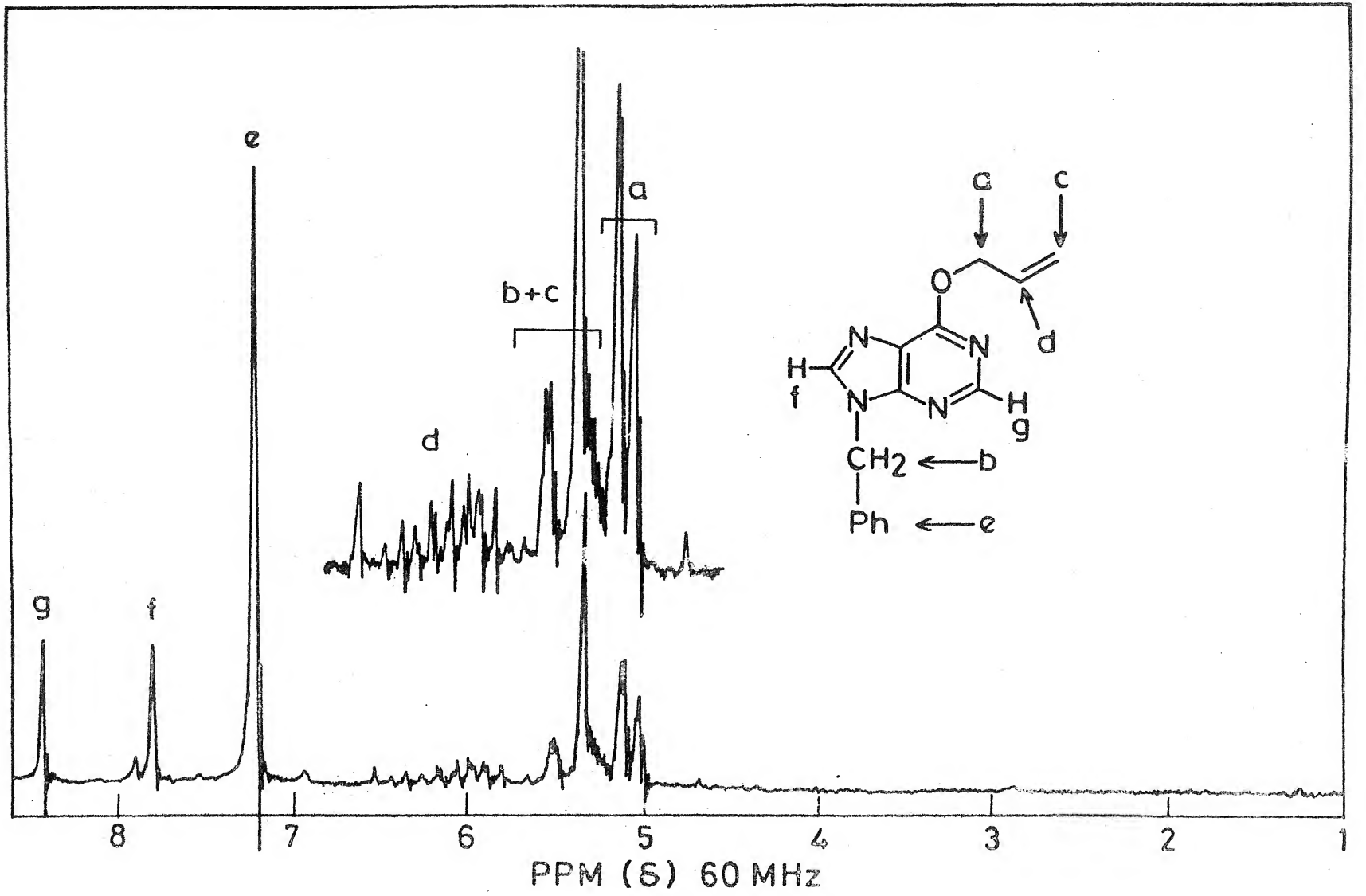

f
e
d
b+c
a
H
d
H
d
H
d
O
N
N
H
e
H
f
b
c
H
N
Ph
a
d
9
8
7
6
5
4
3
PPM (δ) 60MHz

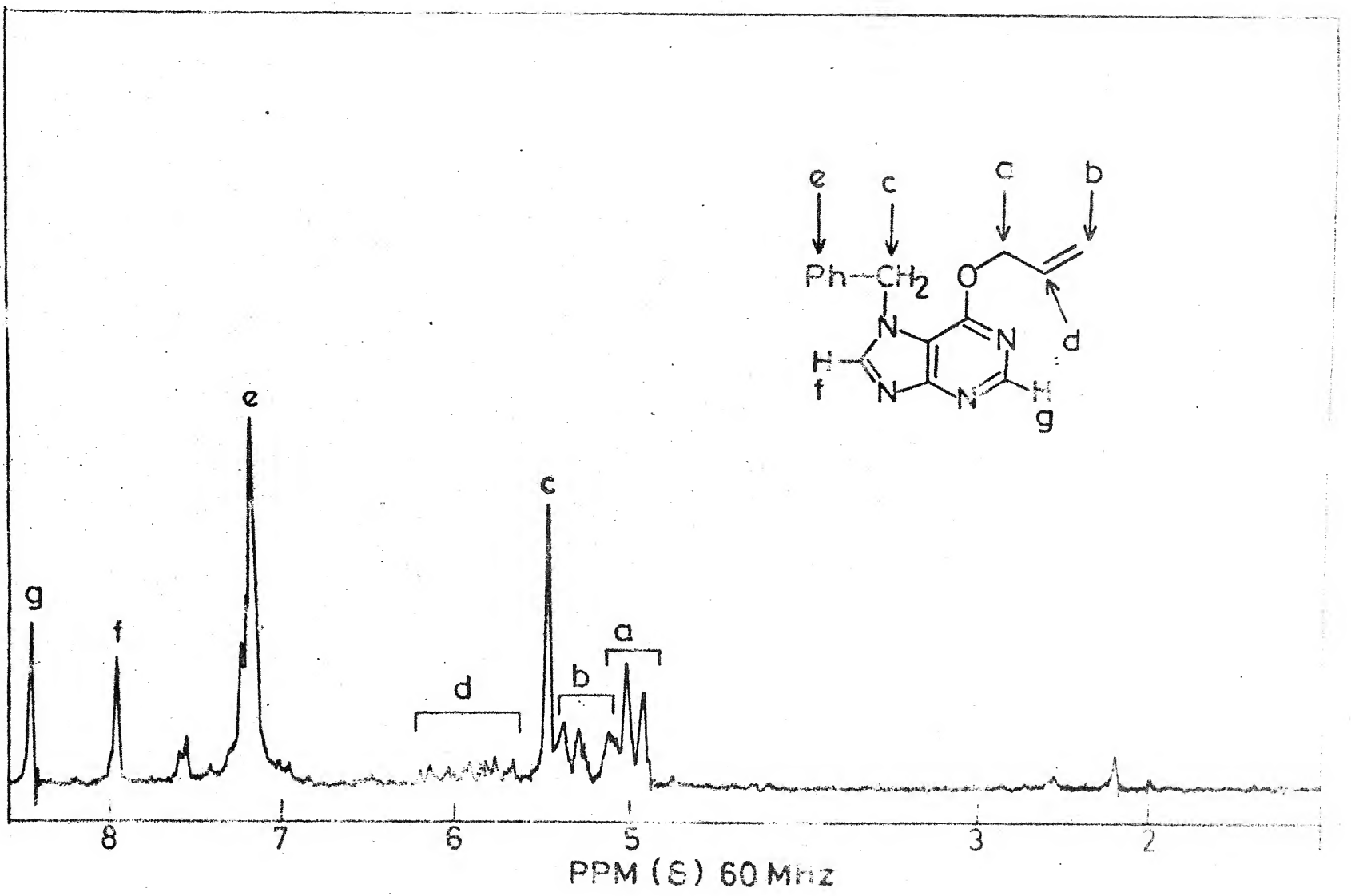

e
d
c
b
a
9
8
7
6
5
4
3
PPM (δ) 100 MHz
e
H
O
a
O2N
NH2
N
H
d
N
H
c
H
b

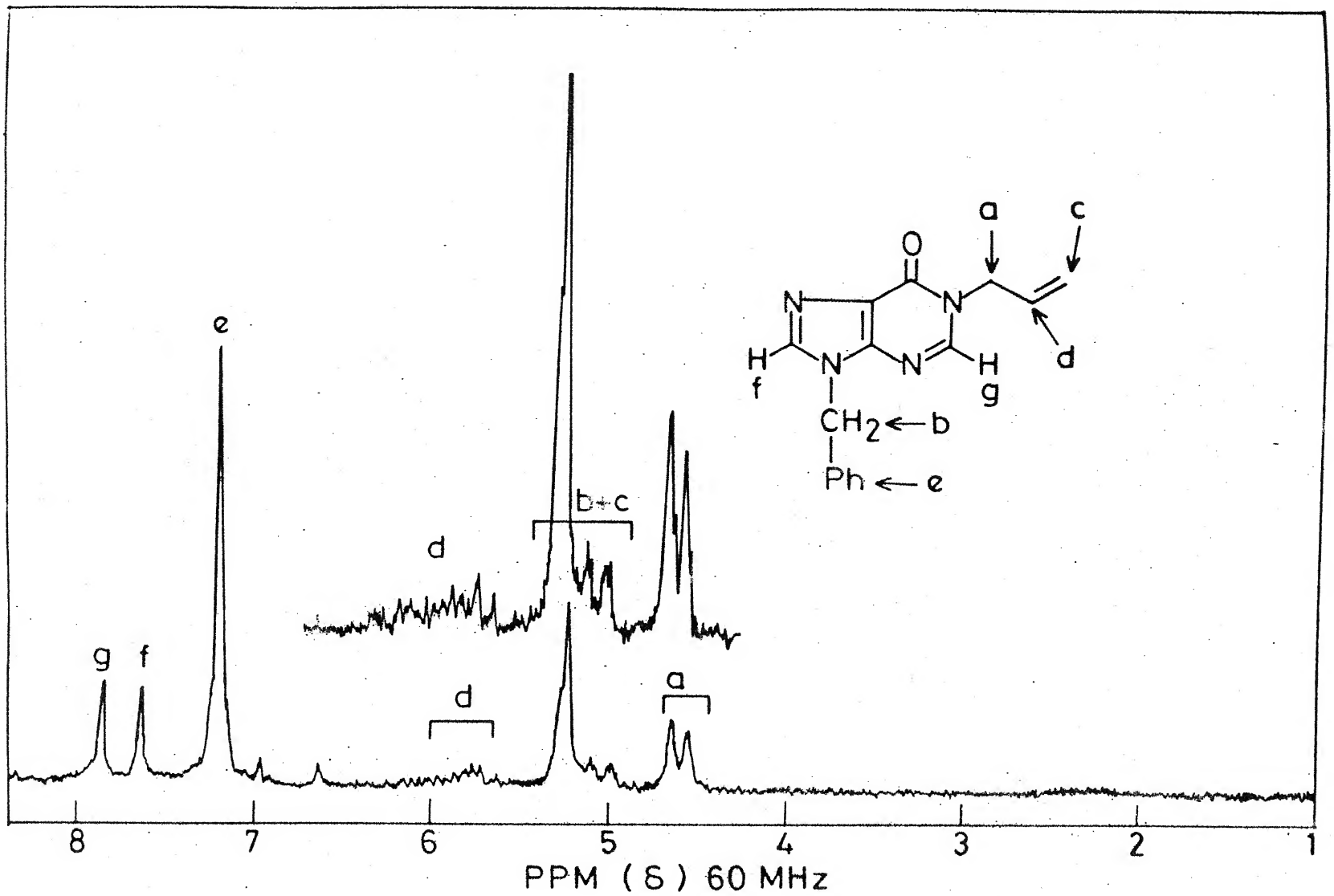

a
b
c
d
e
f
PPM (δ) 100 MHz
4
5
6
7
8
9
NH2 a
NH2 b
H d
H c
H e
H f
O2N

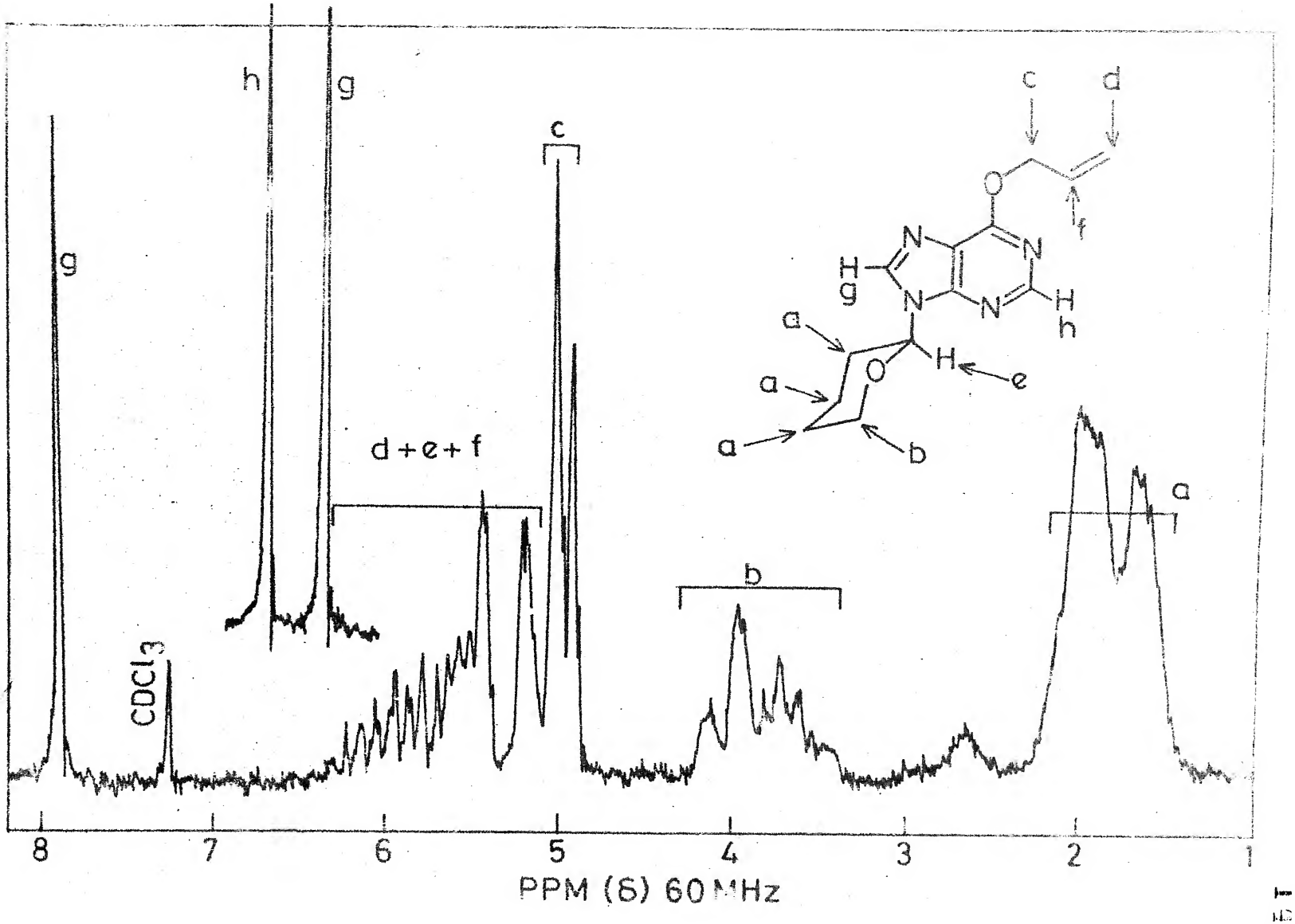

d
8.7 δ
b
Cl
N
N
H
c
N
N
H
d
CH2—Ph
a
b
a
c
8
7
6
5
PPM (δ) 60MHz

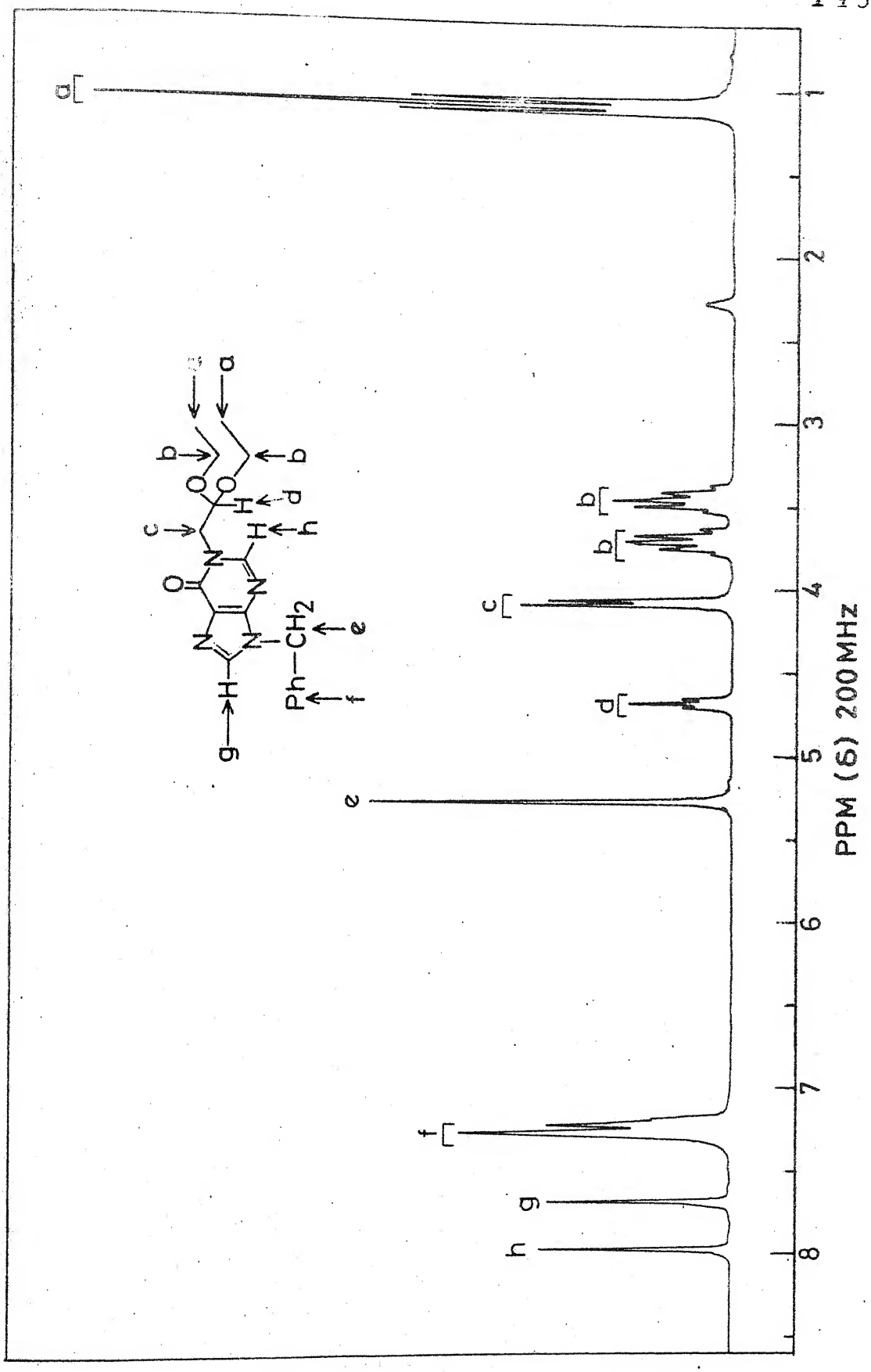

b
a
Cl
Ph–H2C
N
N
H
N
N
H
c
d
b
a
d
c
offset 50
8
7
6
5
PPM (δ) 60 MHz

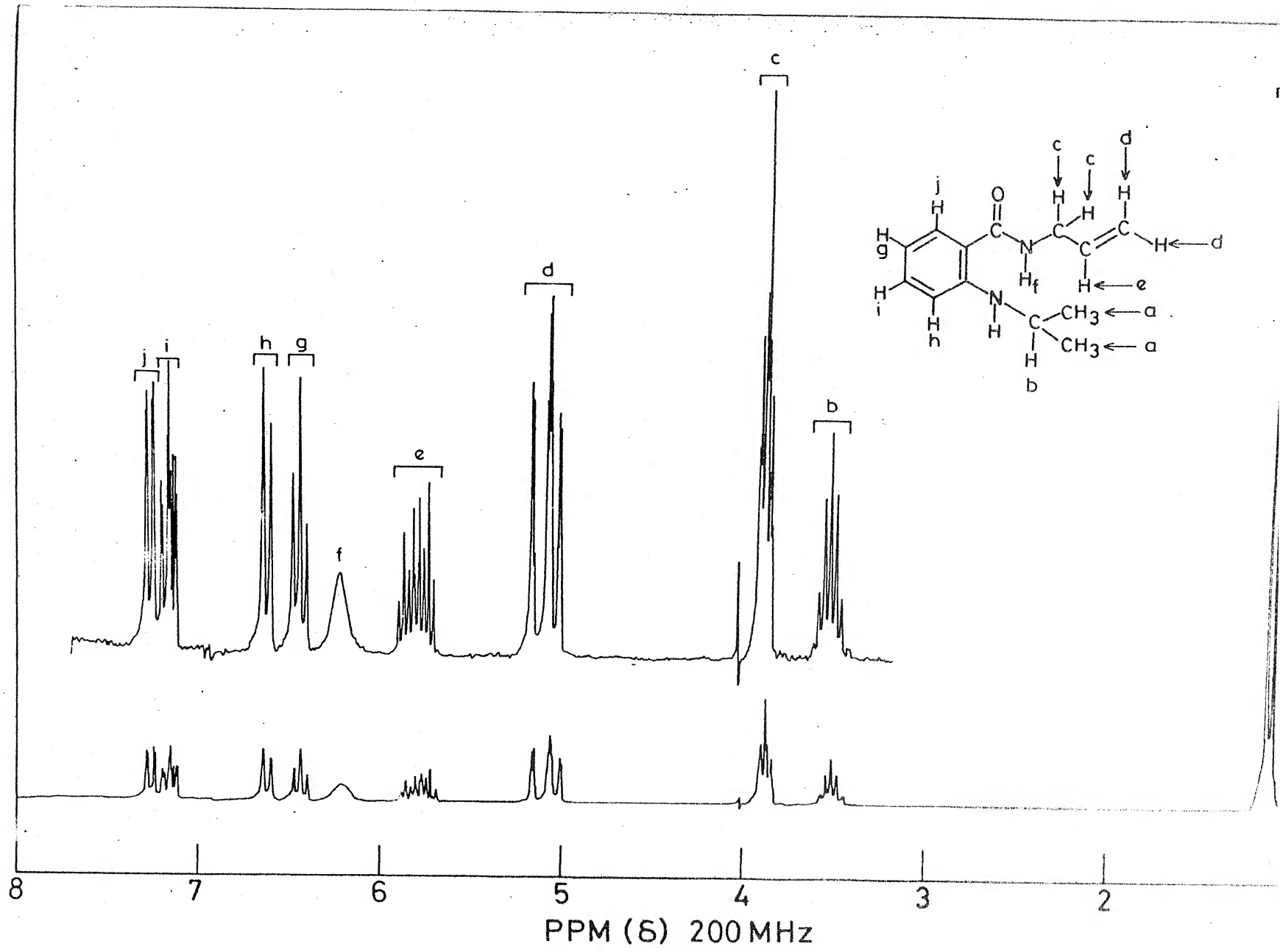

e
a
b+c
d
g
f
a
c
d
O
N
N
H
f
N
N
H
g
CH2 ← b
Ph ← e
8
7
6
5
4
3
2
1
PPM (δ) 60 MHz

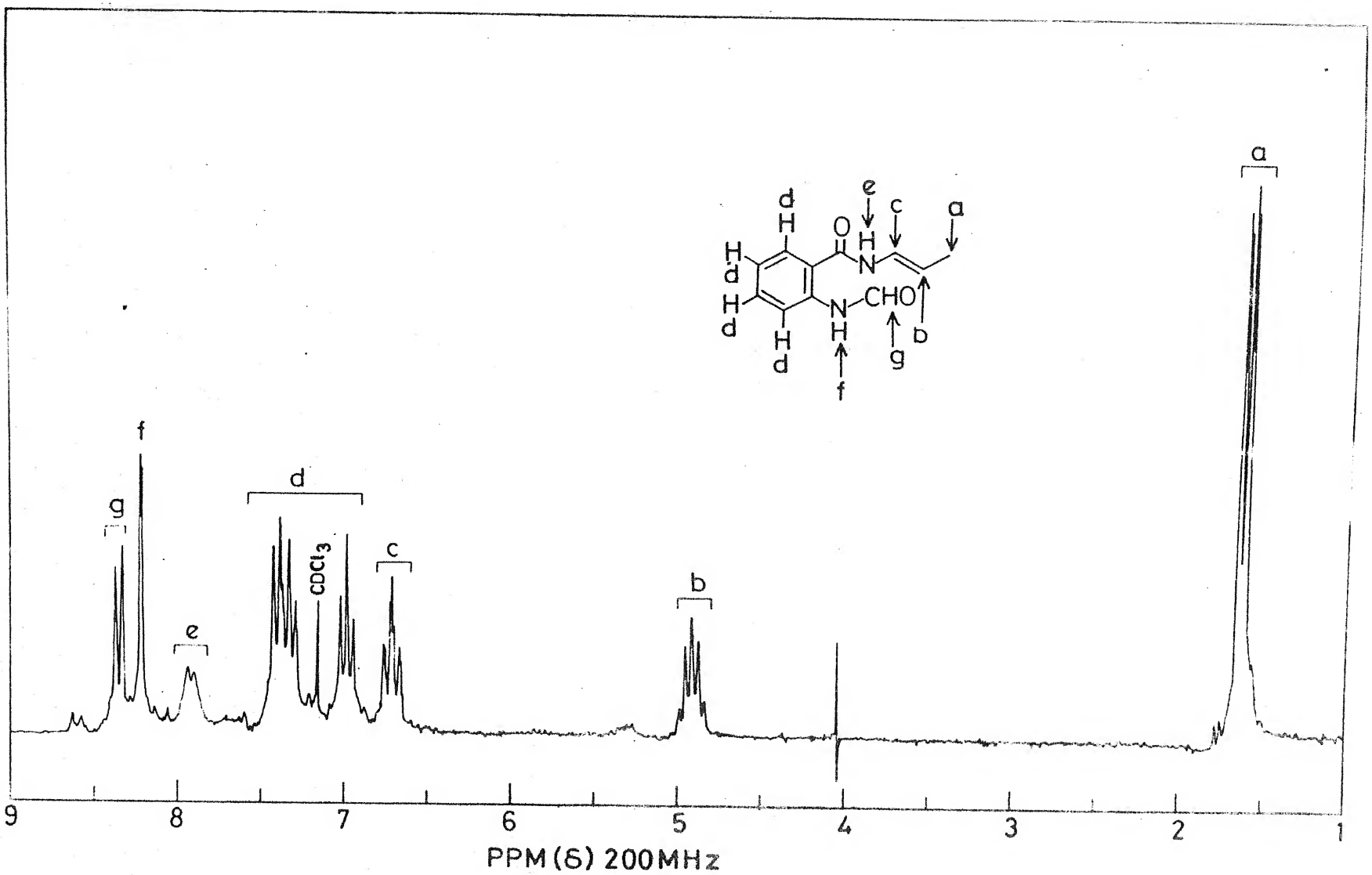

e
c
c
b
Ph–CH2
O
N
N
H
f
N
N
H
g
d
g
f
e
d
c
b
a
8
7
6
5
3
2
PPM (δ) 60 MHz

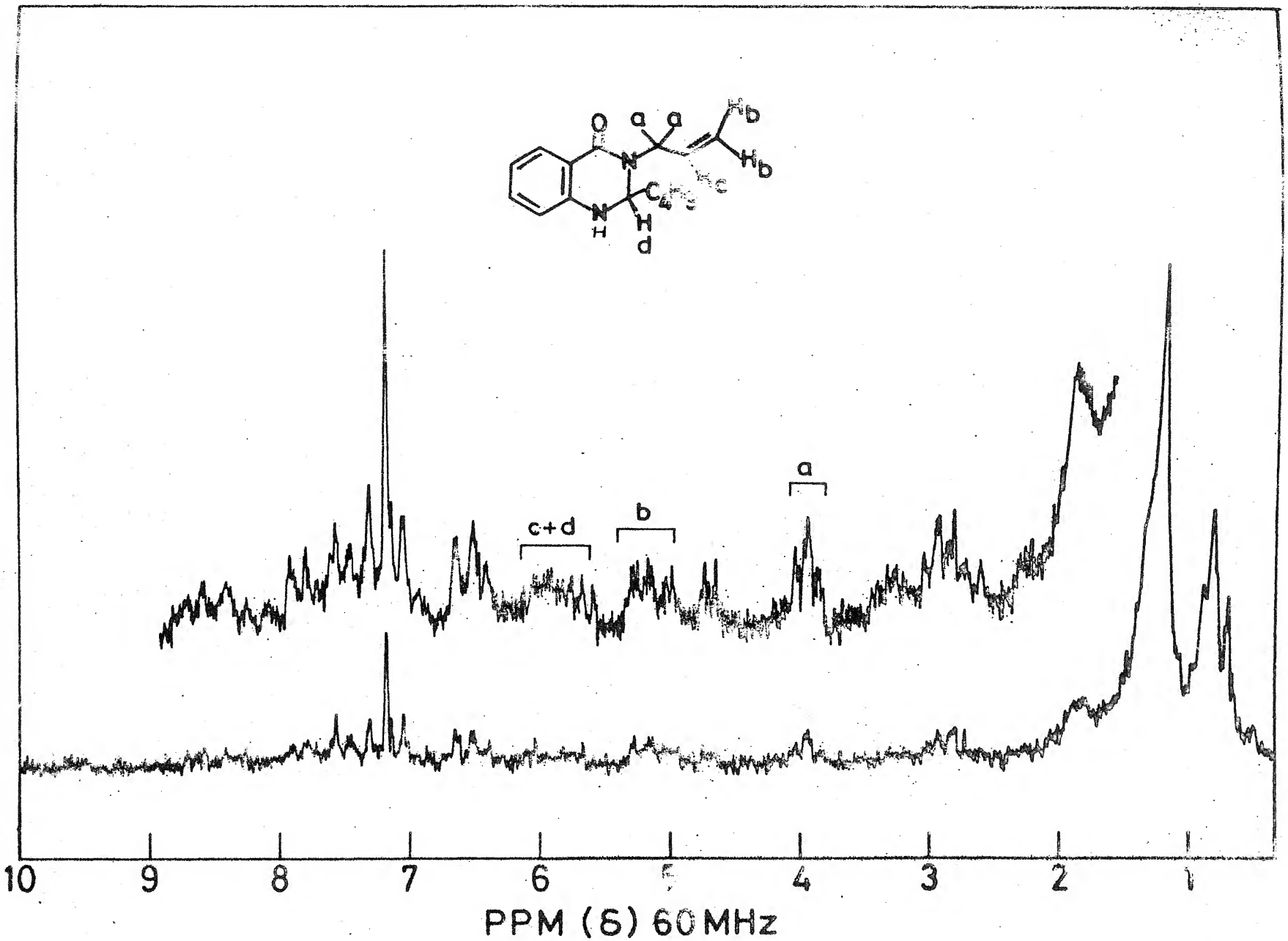

a
c
O
N
N
H
N
N
H
f
g
d
CH2 ← b
Ph ← e
e
b+c
d
g
f
d
a
8
7
6
5
4
3
2
1
PPM (δ) 60 MHz

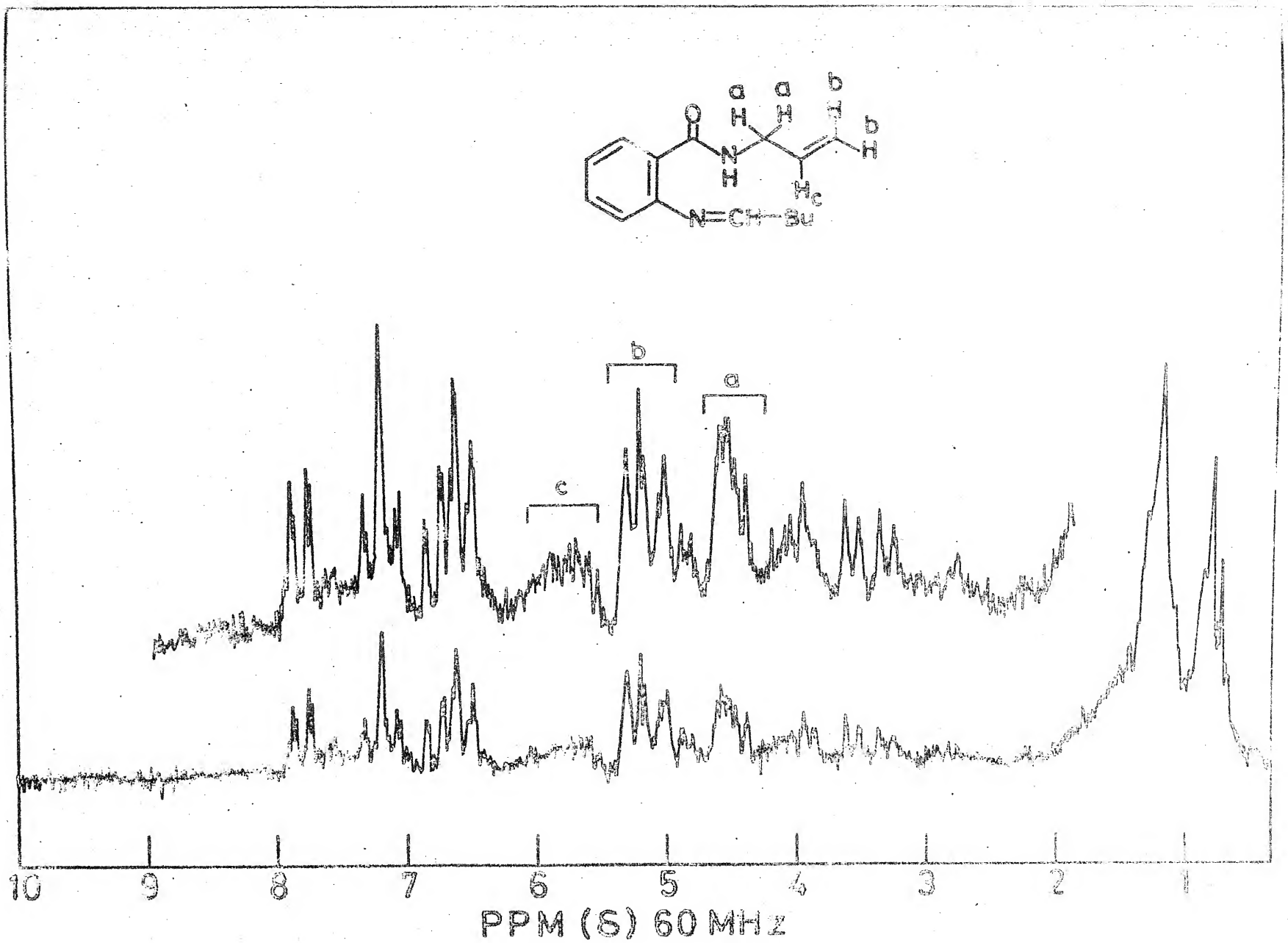

h
g
c
d
g
f
N
N
H
g
N
N
H
h
a
O
H
e
a
a
b
d+e+f
b
a
CDCl3
8
7
6
5
4
3
2
1
PPM (δ) 60 MHz

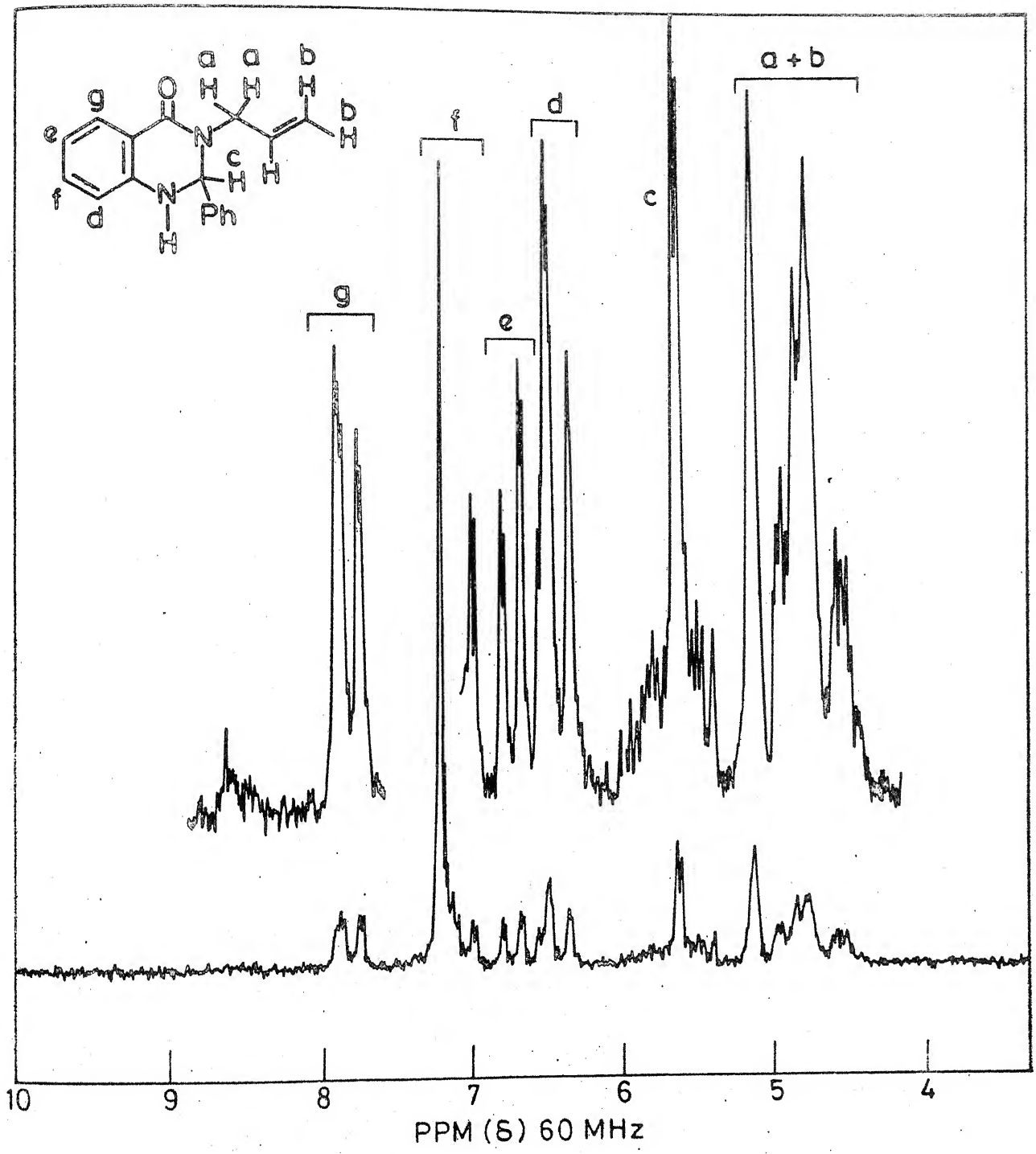

a
b
b
c
d
h
e
Ph—CH2
f
g
a
b
b
c
d
e
f
g
h
1
2
3
4
5
6
7
8
PPM (δ) 200 MHz

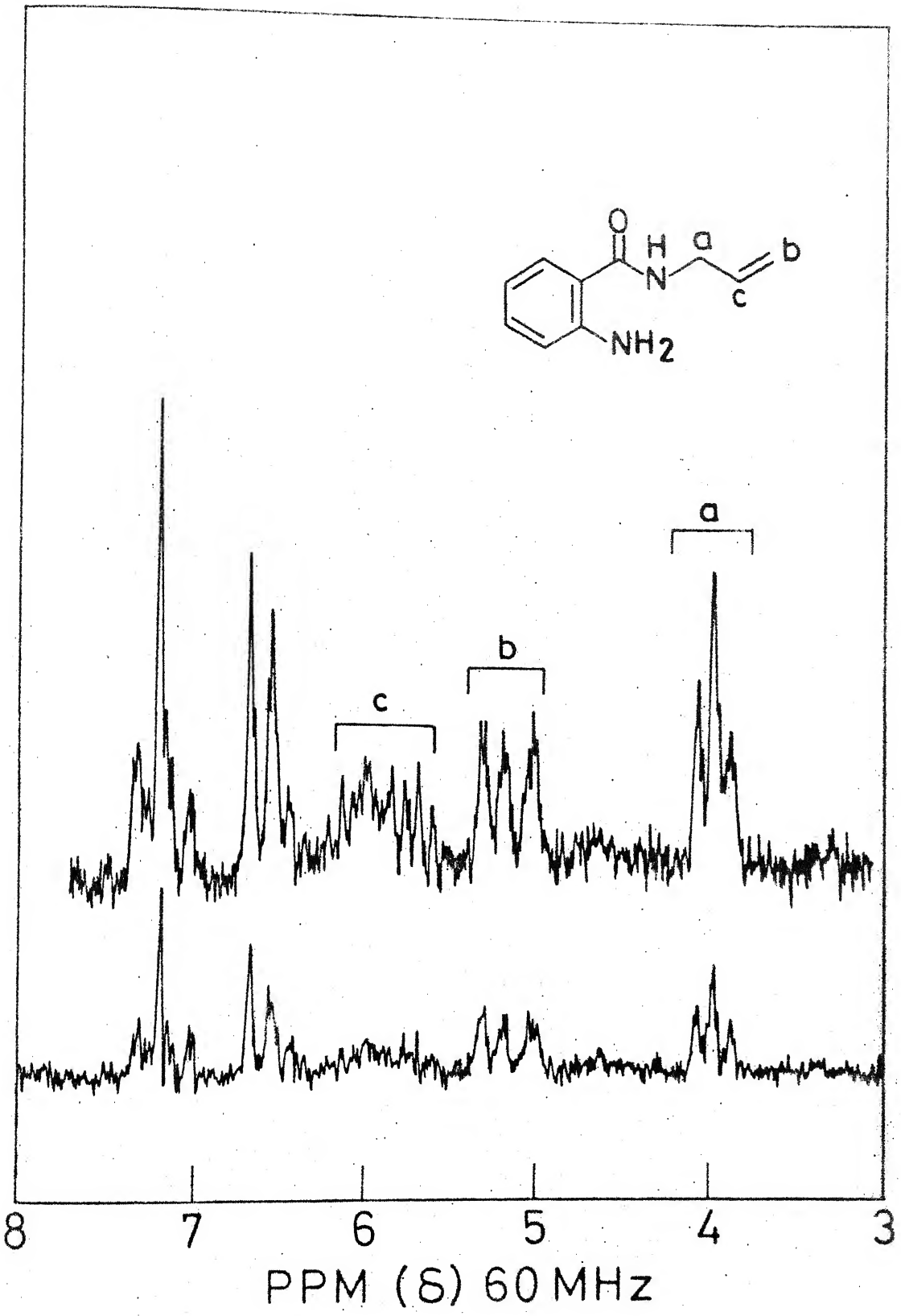

c
d
j
i
h
g
f
e
d
b
8
7
6
5
4
3
2
PPM (δ) 200 MHz

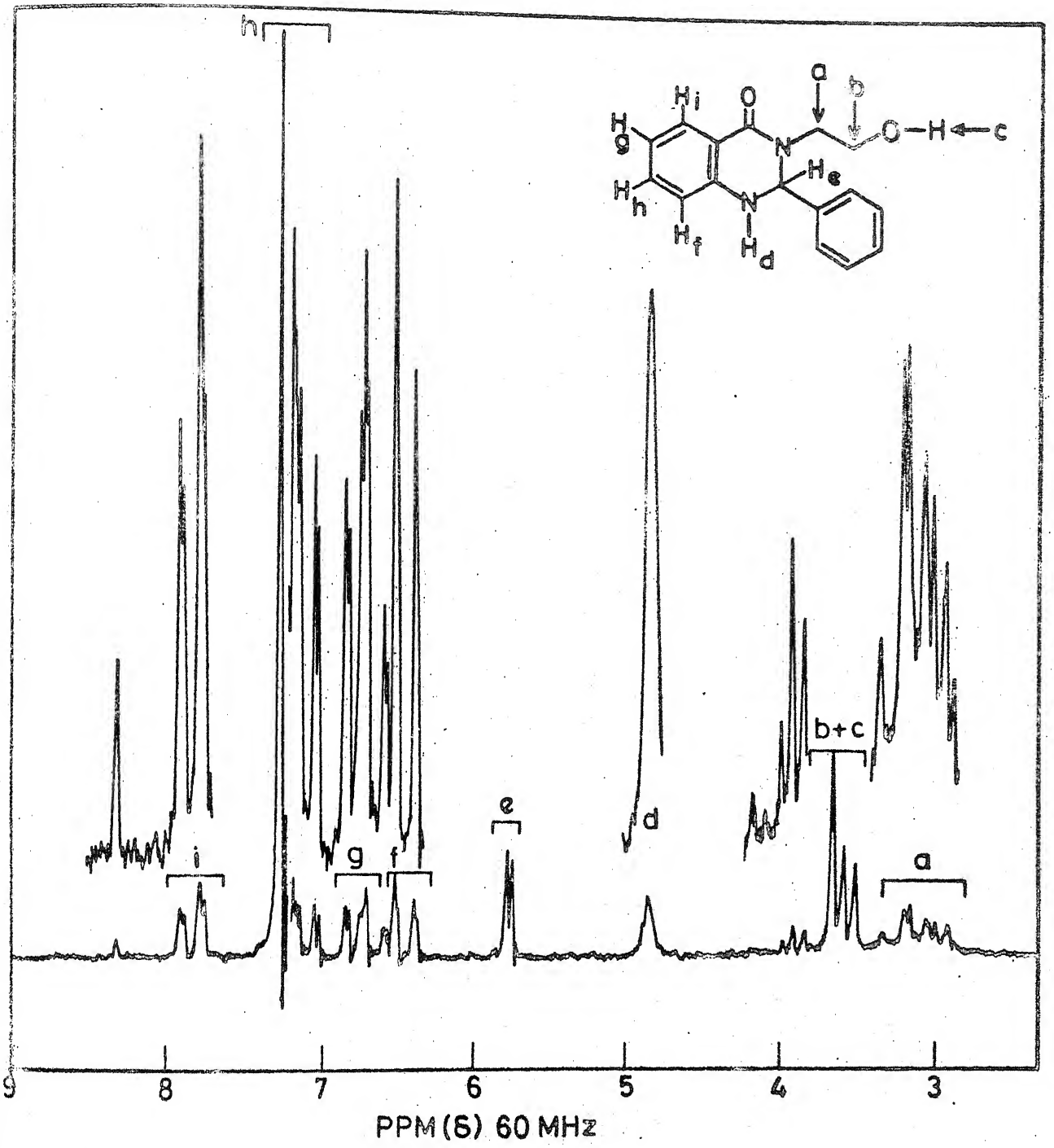

a
b
c
d
e
f
g
CDCl3
9
8
7
6
5
4
3
2
1
PPM (δ) 200MHz

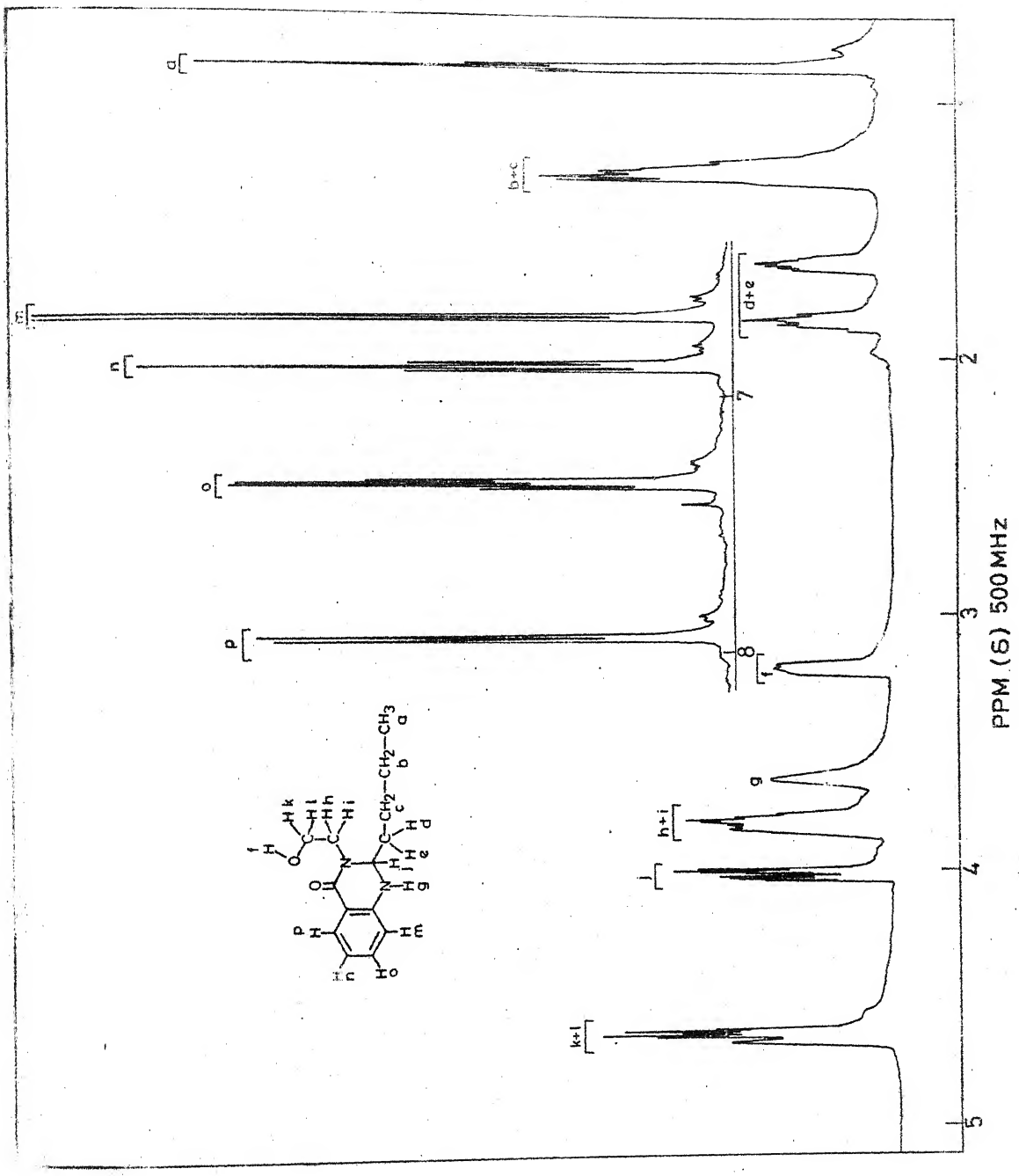

c+d
b
a
10
9
8
7
6
5
4
3
2
1
PPM (δ) 60 MHz

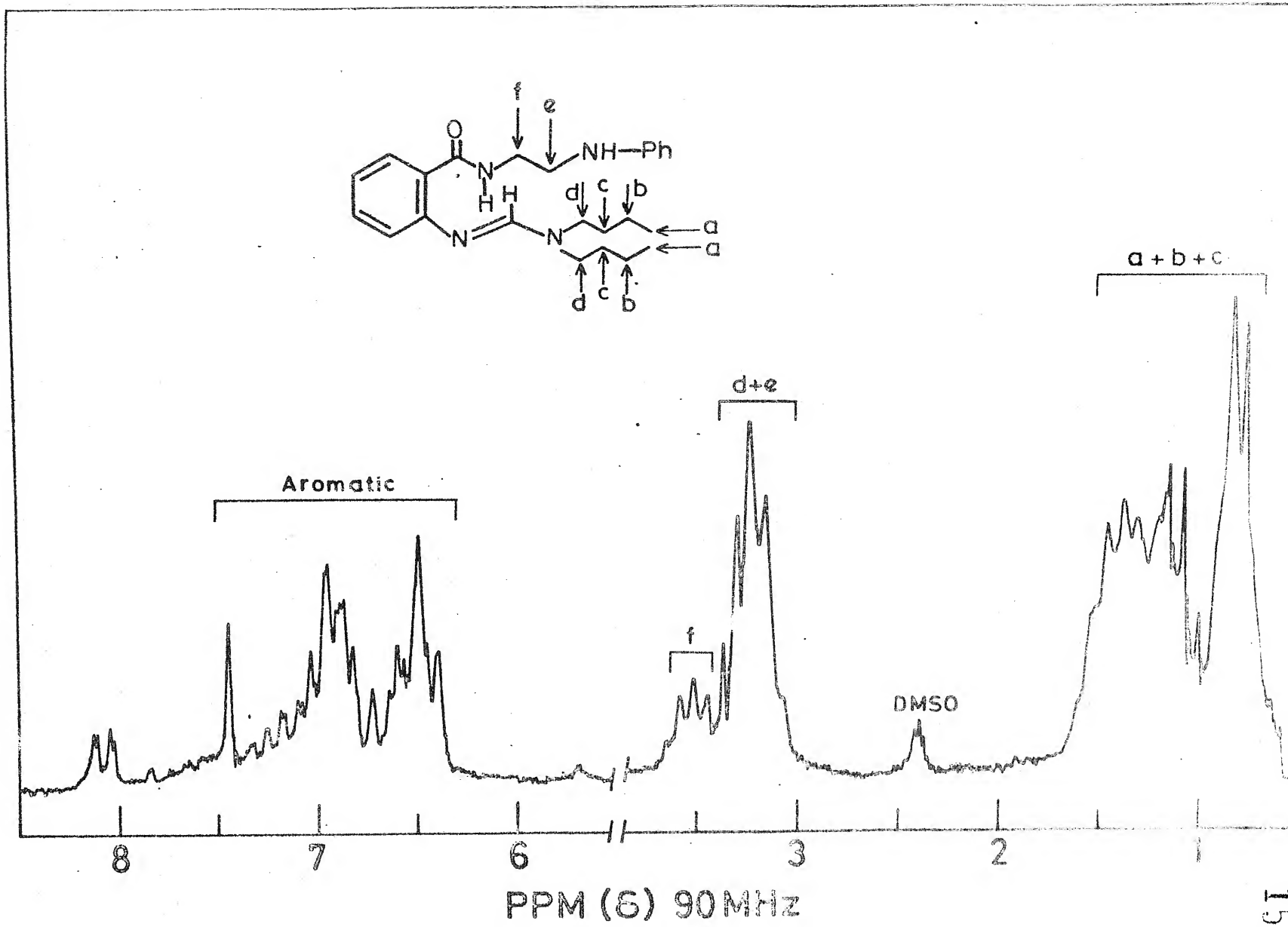

a
a
b
b
O
H
H
H
N
H
Hc
N=CH—Bu
b
a
c
10
9
8
7
6
5
4
3
2
1
PPM (δ) 60 MHz

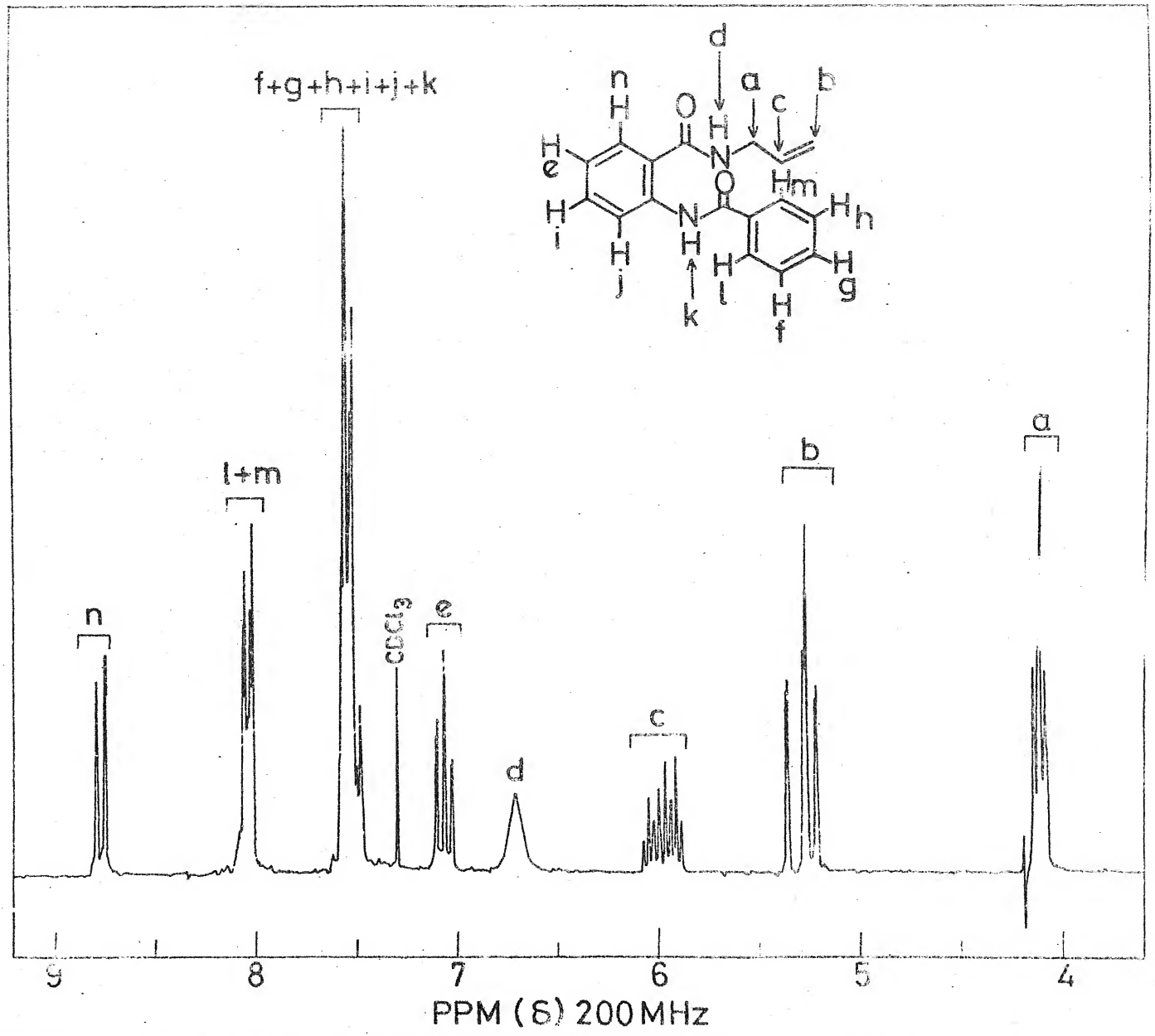

a
a
b
g
O
H
H
H
b
H
e
N
f
c
H
H
d
N
Ph
H
g
f
d
a + b
e
c
10
9
8
7
6
5
4
PPM (δ) 60 MHz

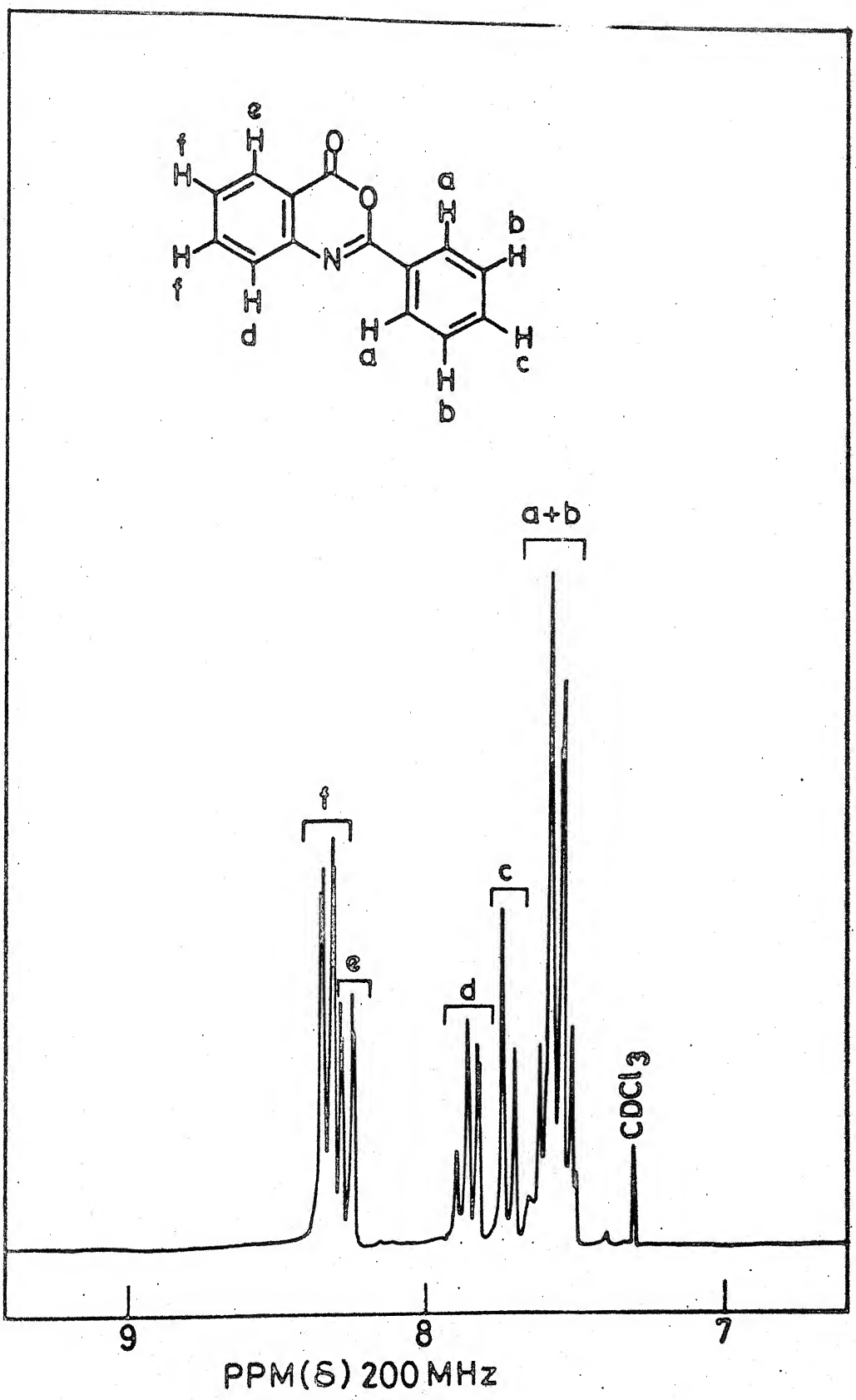

O
H
N
a
b
c
NH2
a
b
c
8
7
6
5
4
3
PPM (δ) 60 MHz

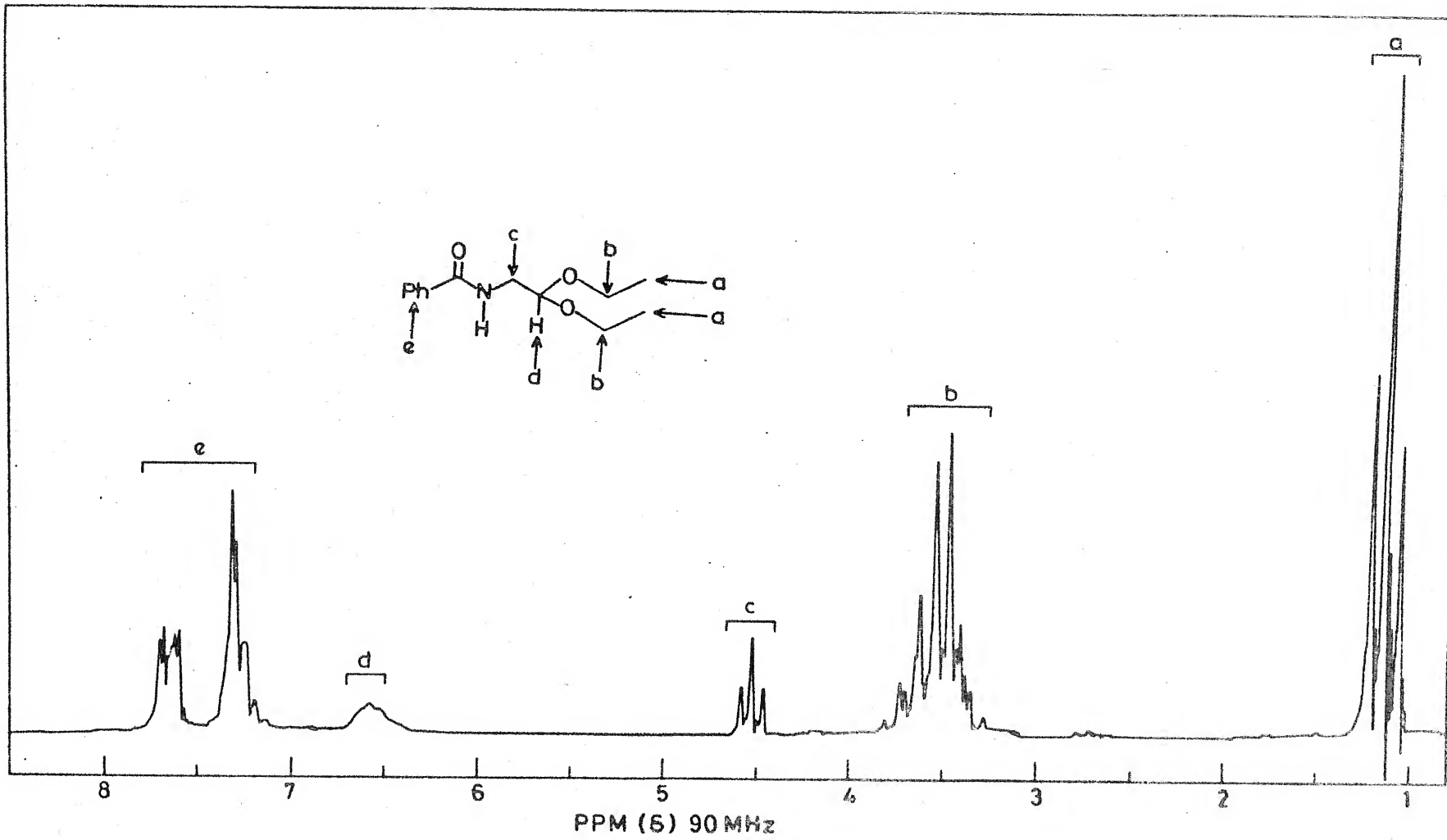

h
i
g
f
e
d
b+c
a
9
8
7
6
5
4
3
PPM (δ) 60 MHz
a
b
c
O
N
O-H
Hi
Hg
Hh
Hf
Hd
He

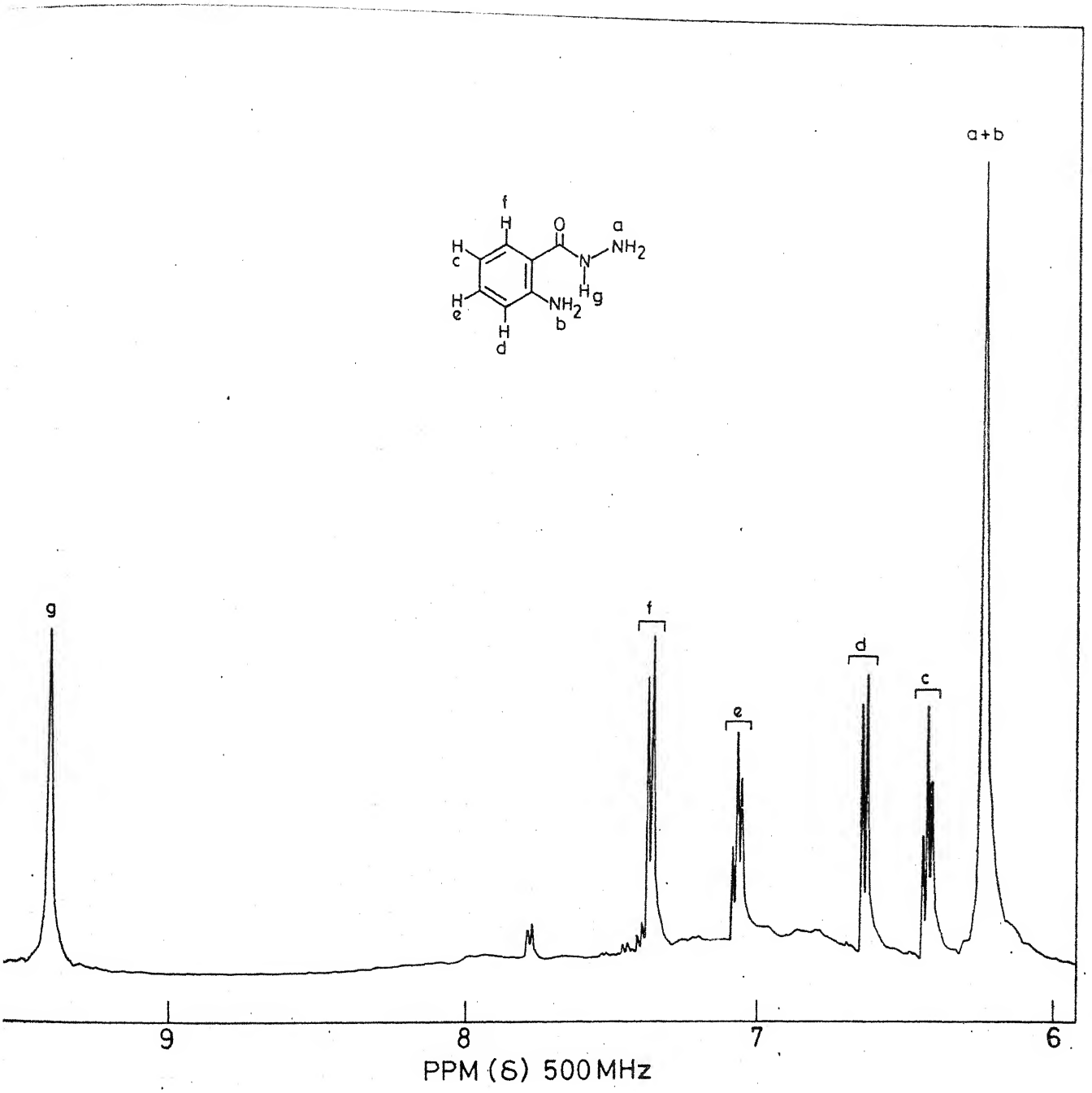

a
b+c
d+e
n
o
p
f
g
h+i
j
k+l
PPM (δ) 500 MHz
1
2
3
4
5
7
8
CH2—CH2—CH3
a
b
c
d
e
f
g
h
i
k
l
m
n
o
p

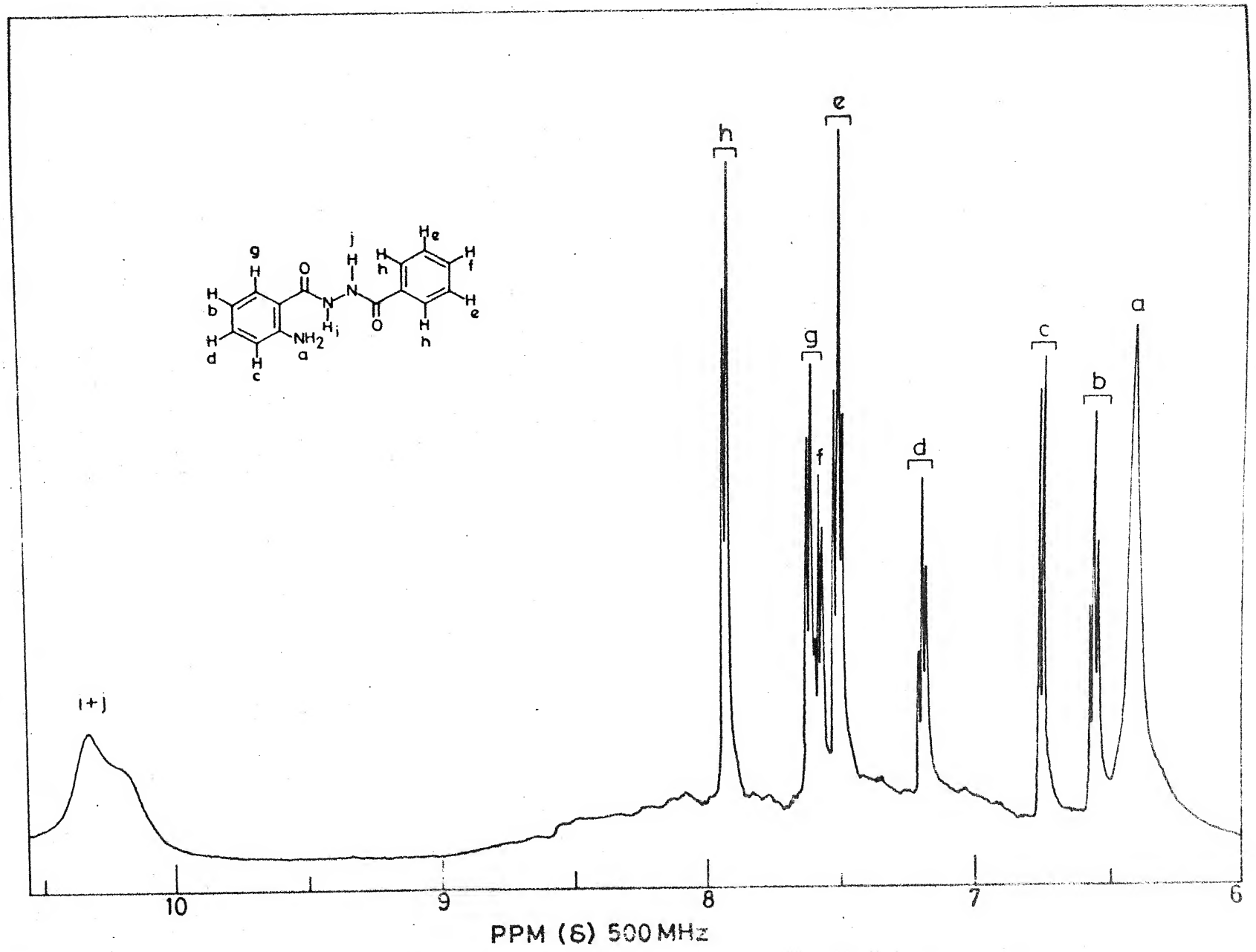

f
e
O
NH—Ph
N
H
H
d
c
b
a
a
N
N
d
c
b
a+b+c
d+e
Aromatic
f
DMSO
8
7
6
3
2
PPM (δ) 90 MHz

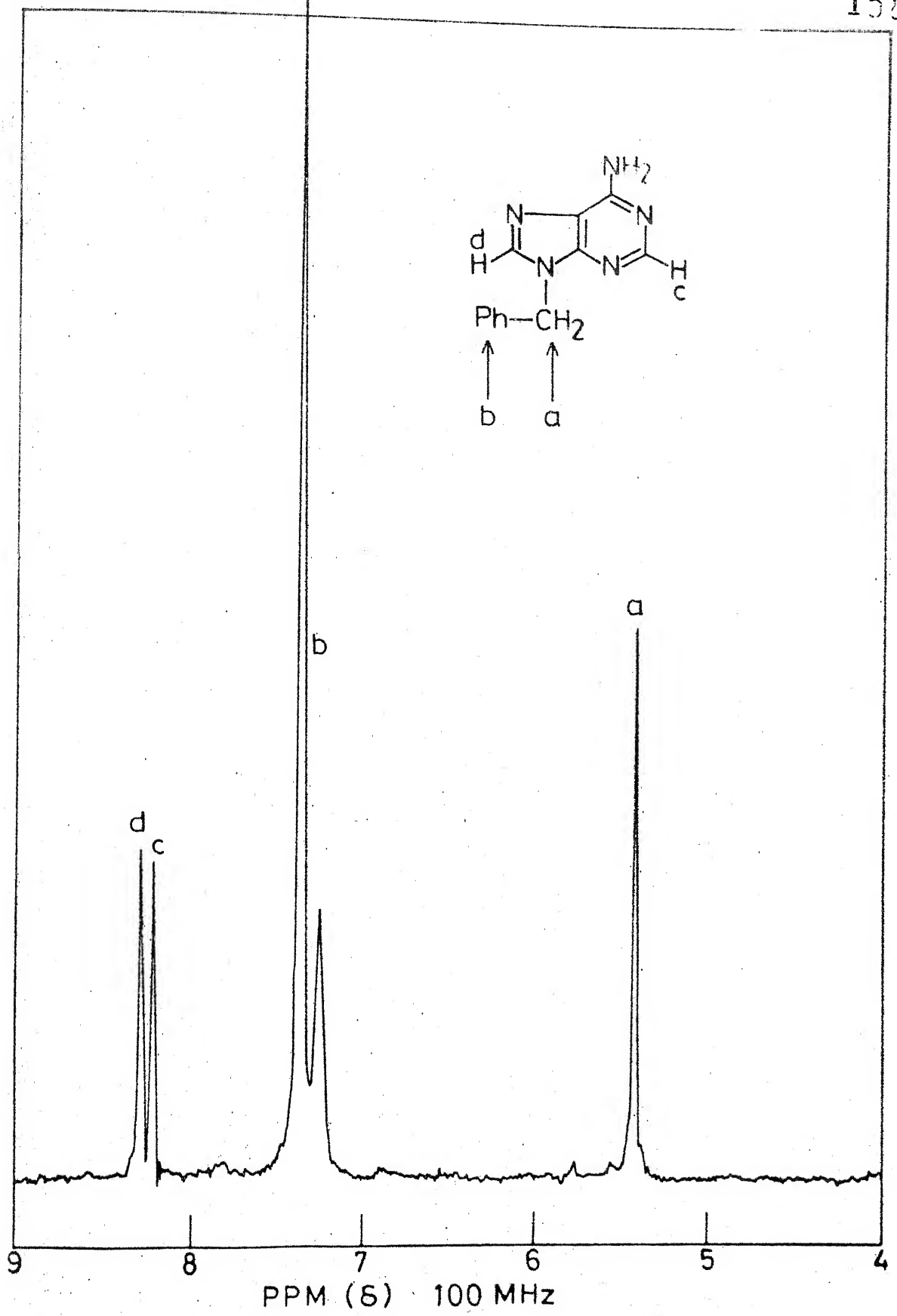

f+g+h+i+j+k
l+m
n
CDCl3
e
d
c
b
a
9
8
7
6
5
4
PPM (δ) 200 MHz

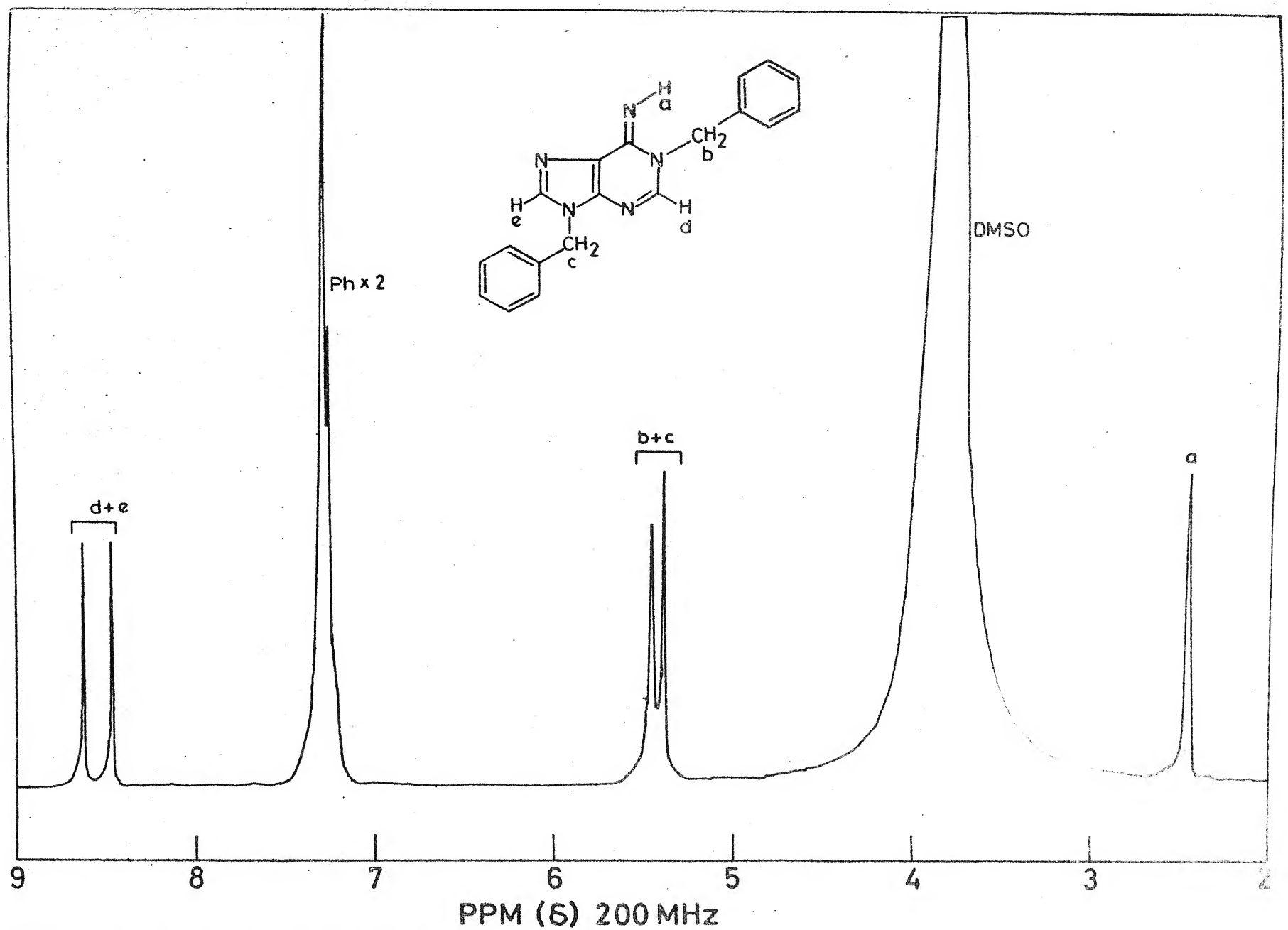

e
H
f
H
O
a
H
b
H
O
N
H
f
H
d
H
a
H
c
H
b
a+b
f
e
d
c
CDCl3
9
8
7
PPM(δ) 200 MHz

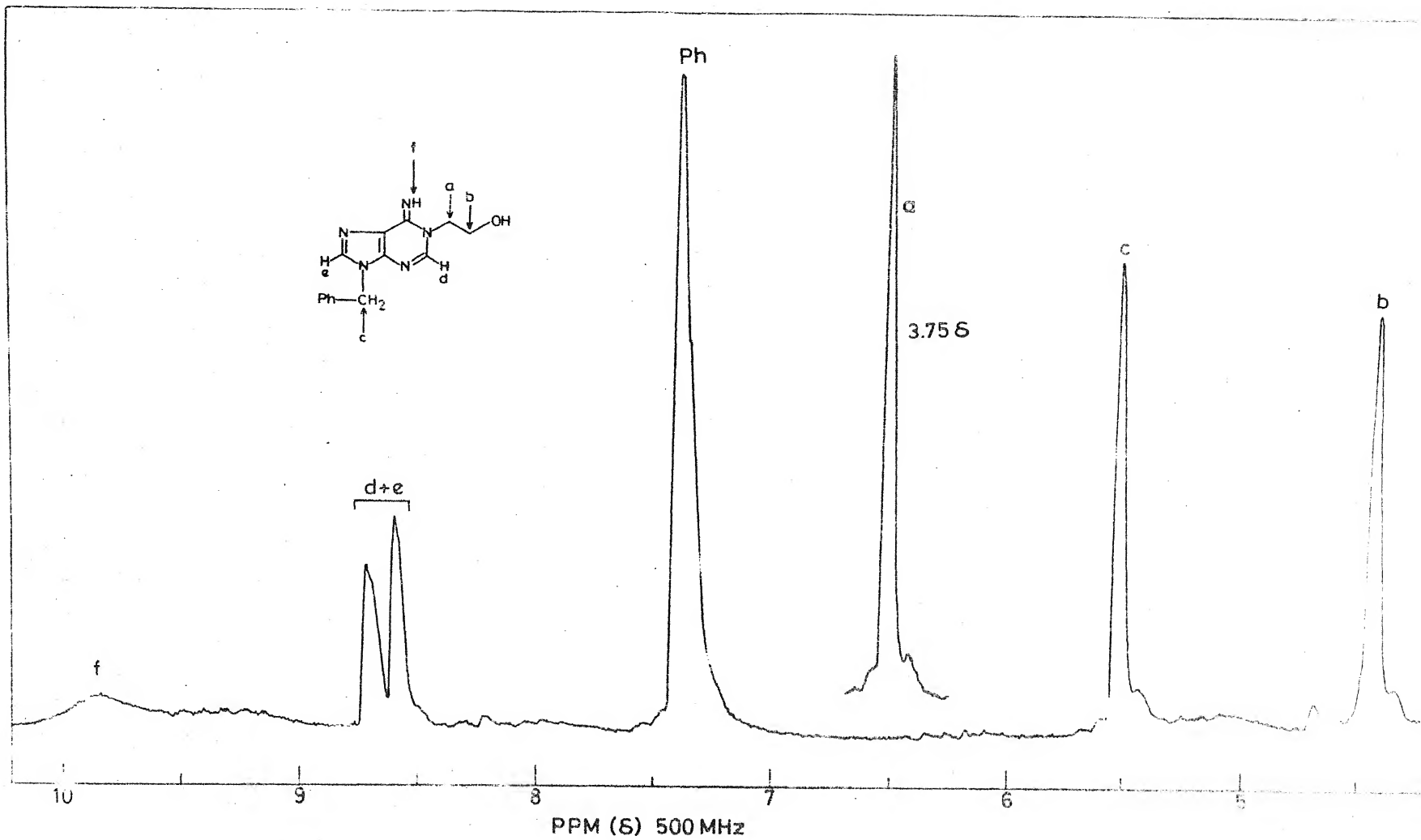

a
b
c
d
e
Ph
O
N
H
O
O
H
a
a
b
b
8
7
6
5
4
3
2
1
PPM (δ) 90 MHz

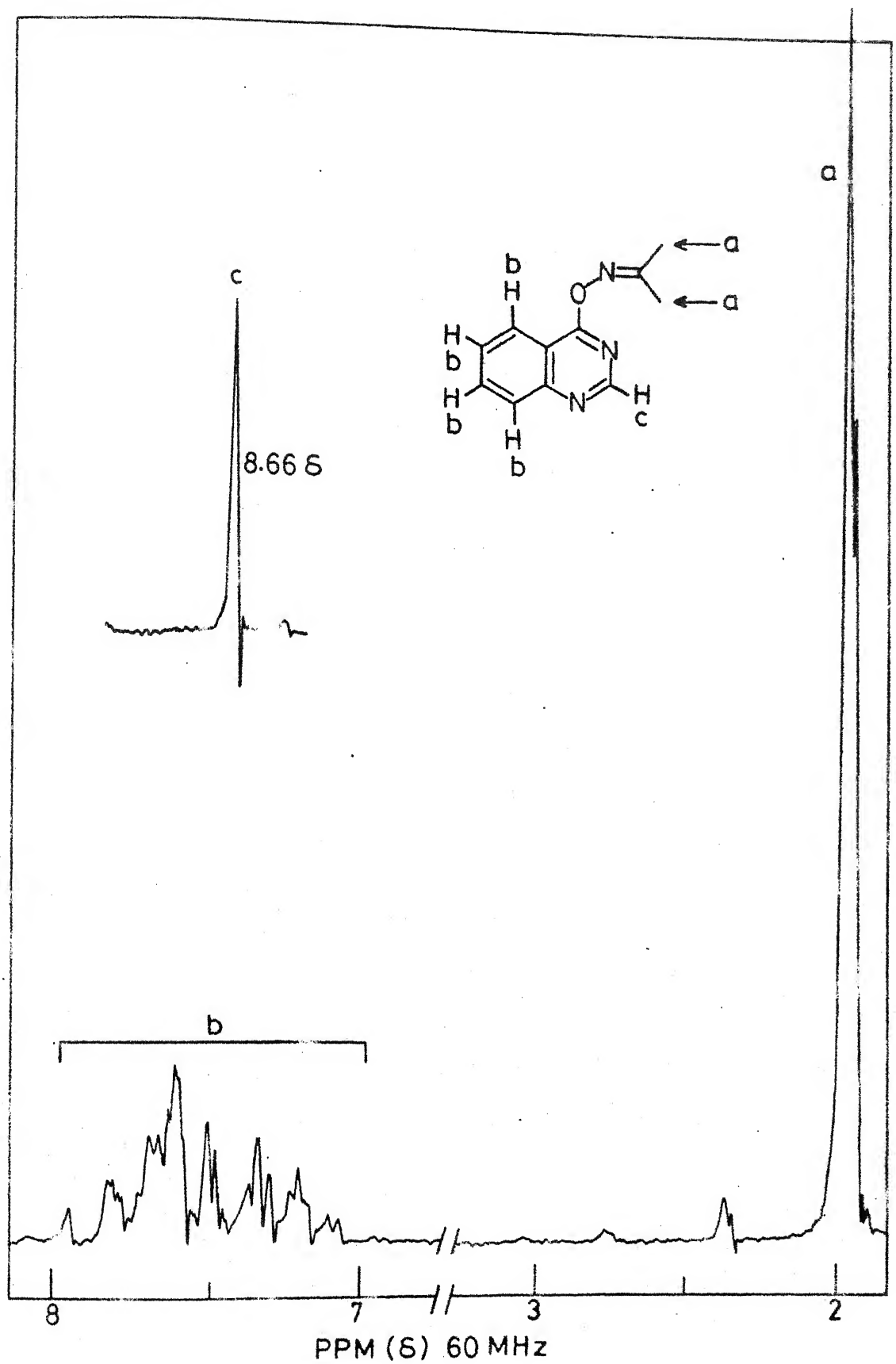

f
H
O
a
NH2
H
c
N
H
g
H
e
NH2
b
H
d
a+b
g
f
e
d
c
9
8
7
6
PPM (δ) 500 MHz

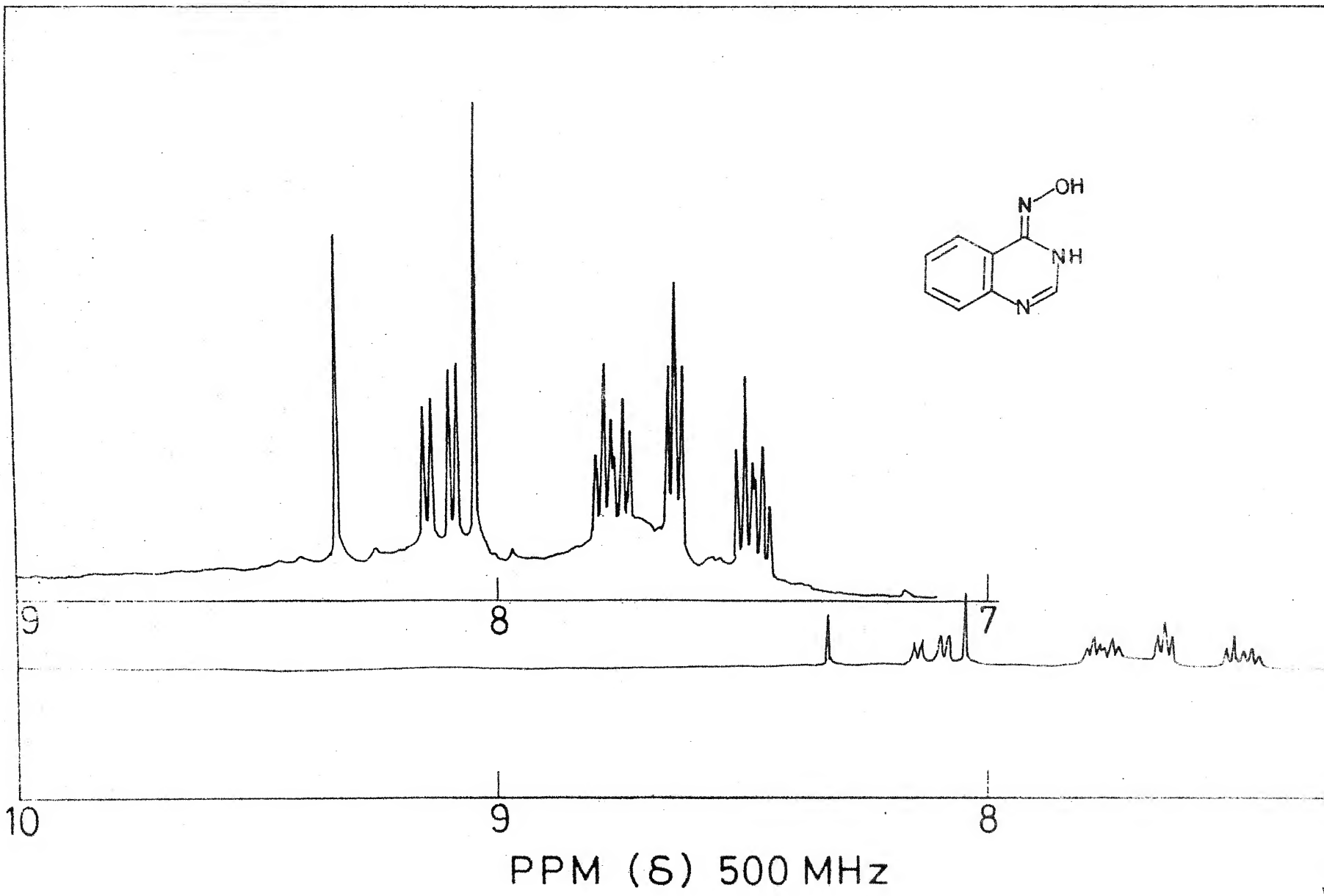

h
e
g
f
d
c
b
a
(i+j)
10
9
8
7
6
PPM (δ) 500 MHz

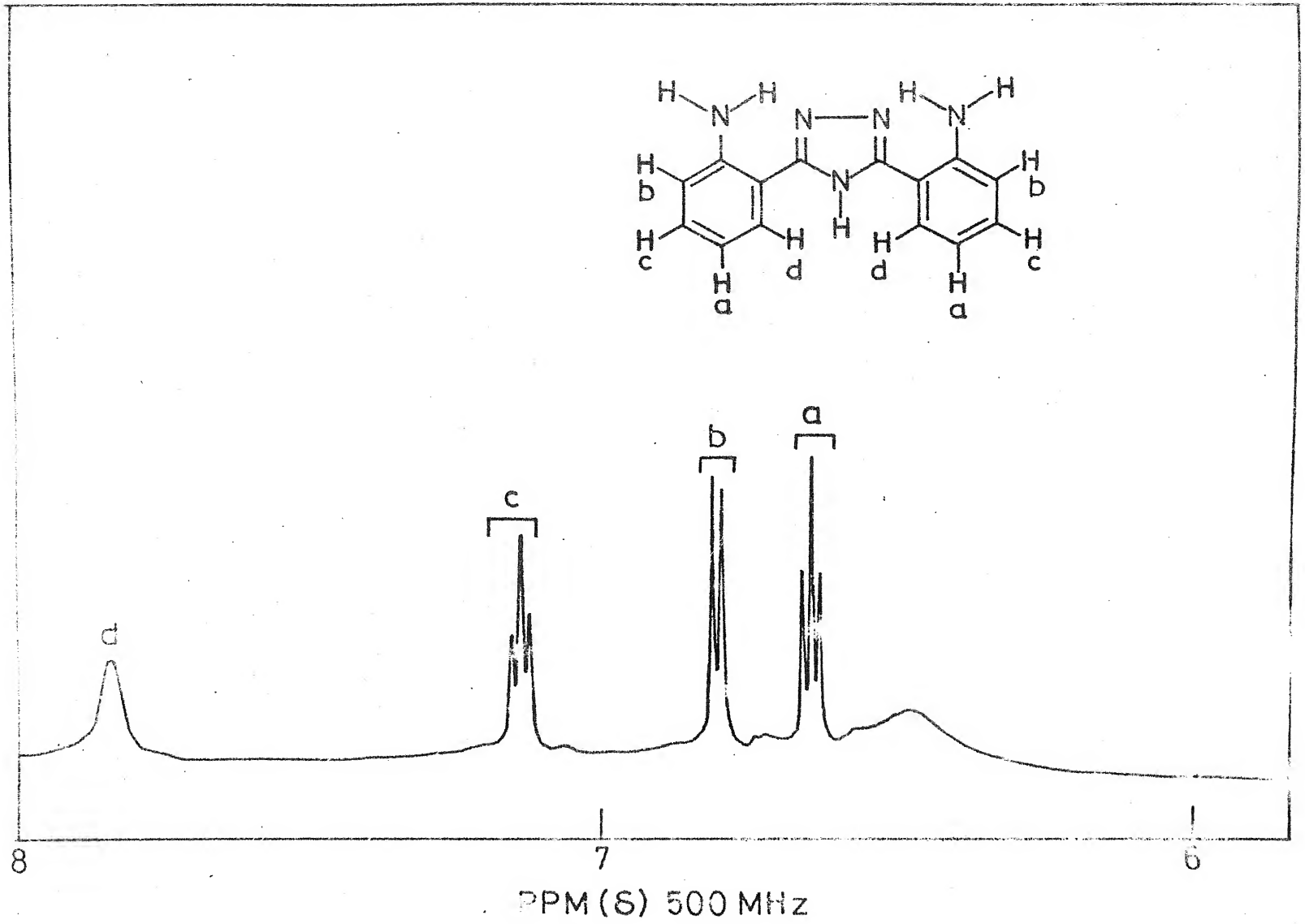

NH2
N
N
d
H
N
N
H
c
Ph—CH2
b
a
a
b
d
c
9
8
7
6
5
4
PPM (δ) 100 MHz

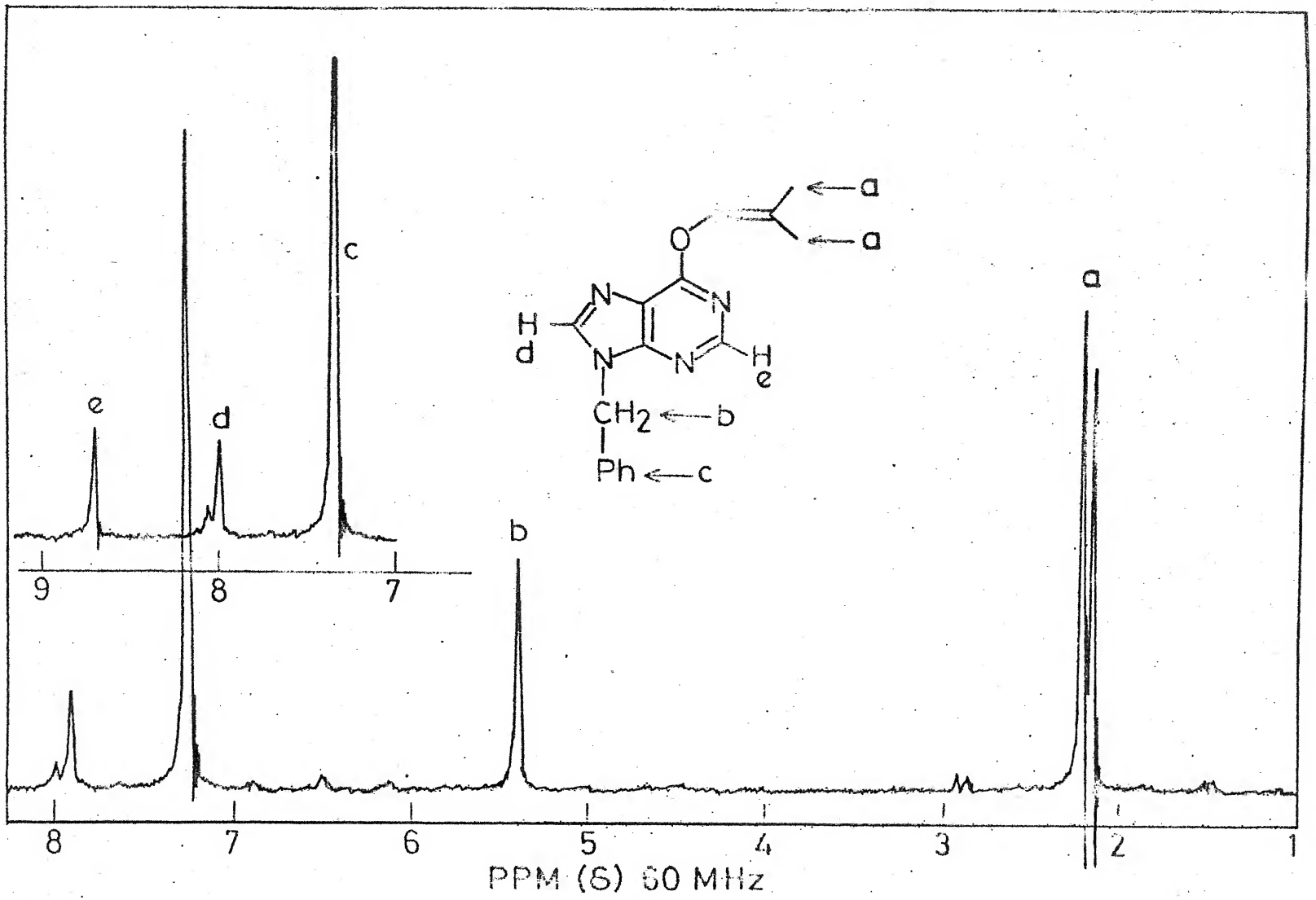

Ph x 2
DMSO
d+e
b+c
a
9
8
7
6
5
4
3
PPM (δ) 200 MHz

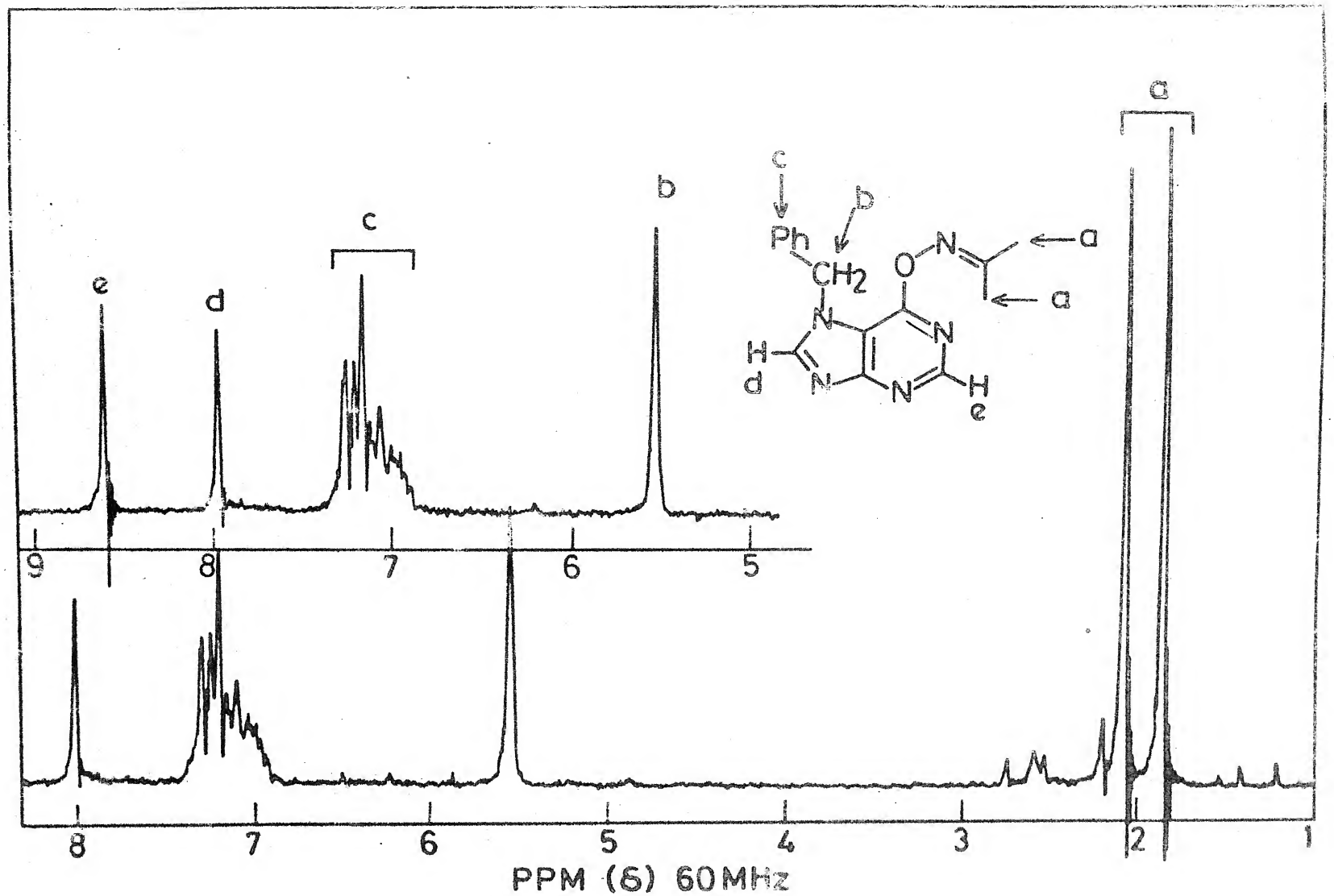

f
a
b
NH
OH
N
N
N
N
H
e
H
d
Ph—CH2
c
Ph
a
3.75 δ
c
b
d÷e
f
10
9
8
7
6
5
PPM (δ) 500 MHz

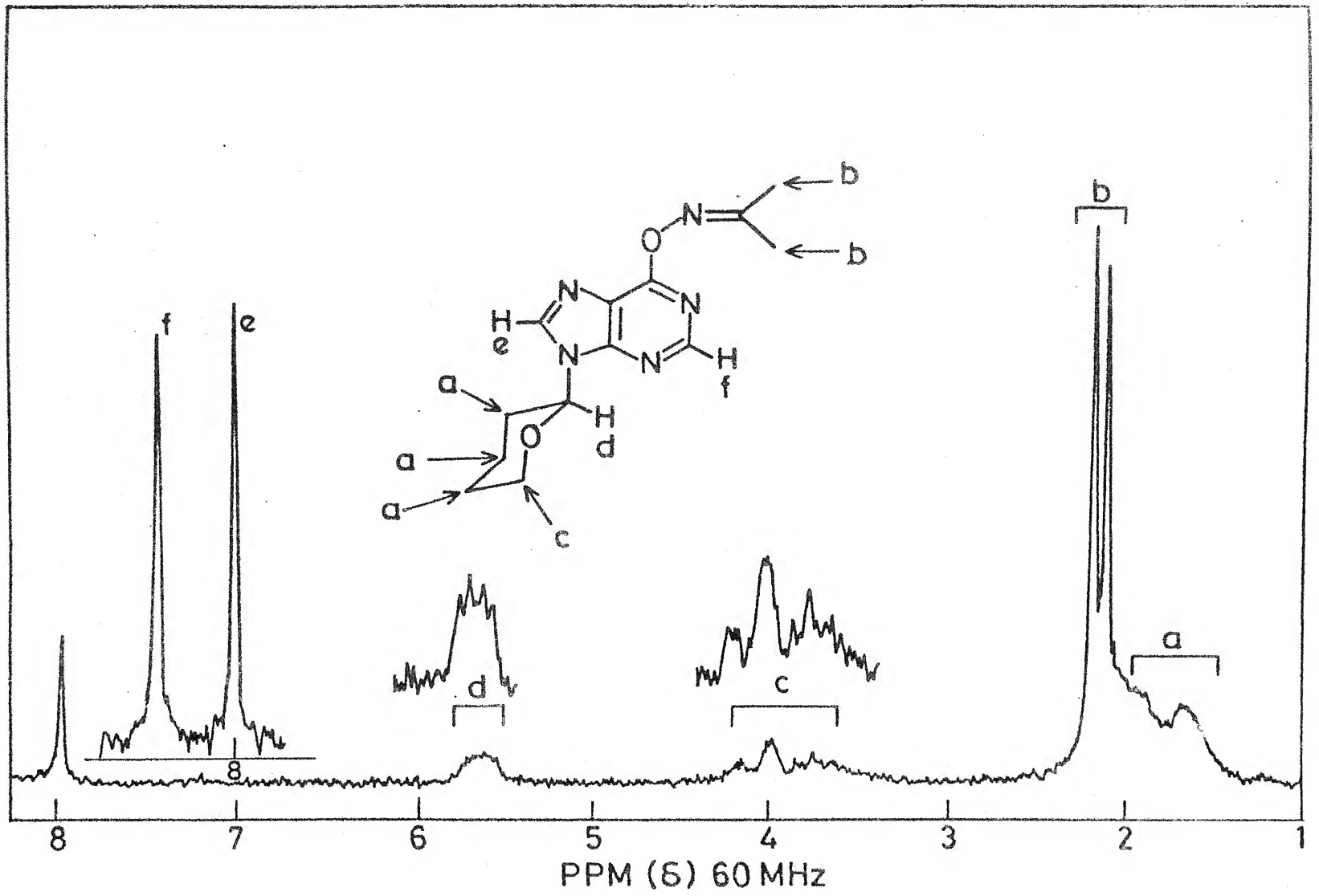

a
c
8.66 δ
b
H
O
N
a
a
H
b
H
b
H
b
N
N
H
c
b
8
7
3
2
PPM (δ) 60 MHz

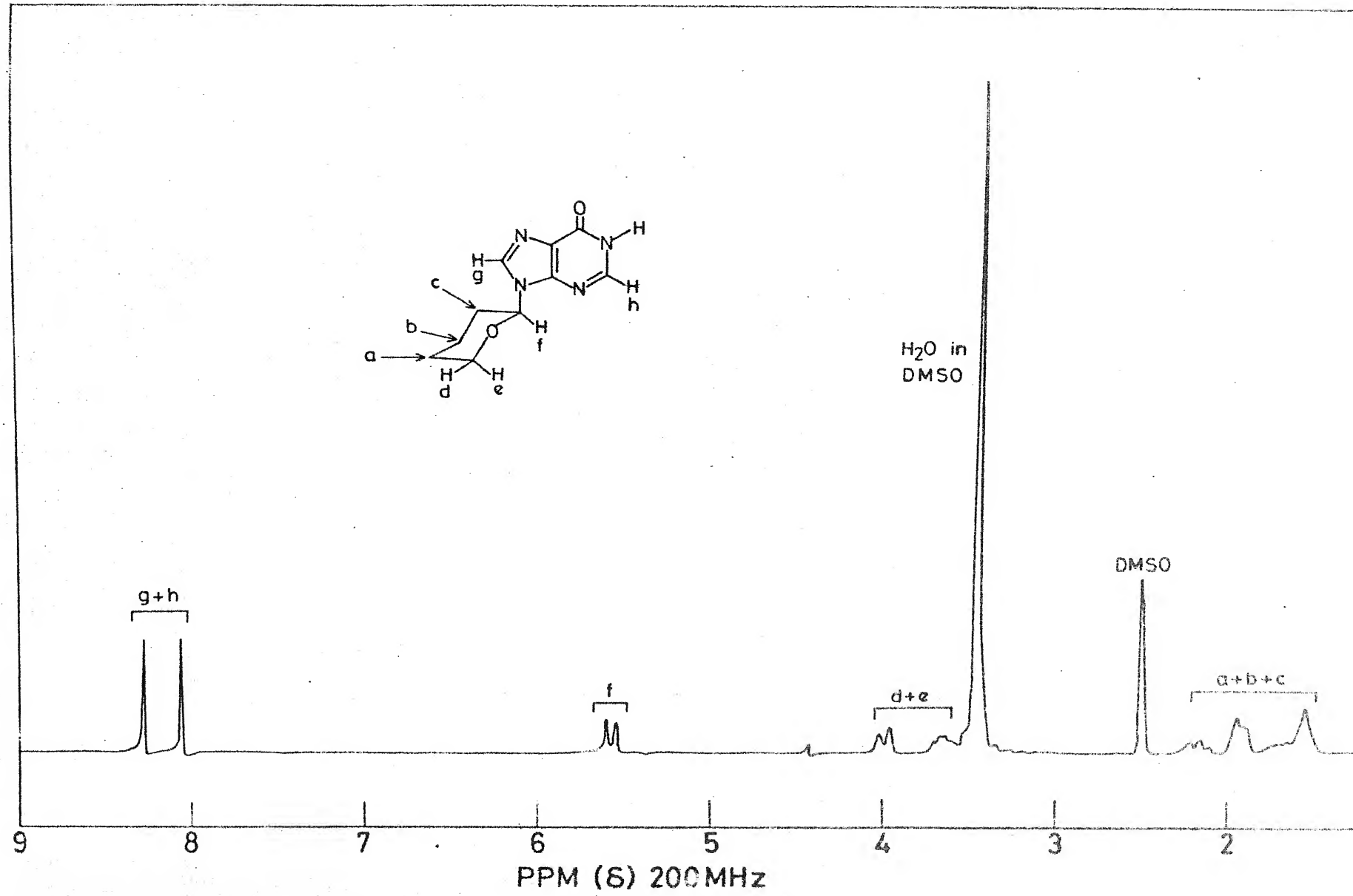

OH
N
NH
N
9
8
7
10
9
8
PPM (δ) 500 MHz

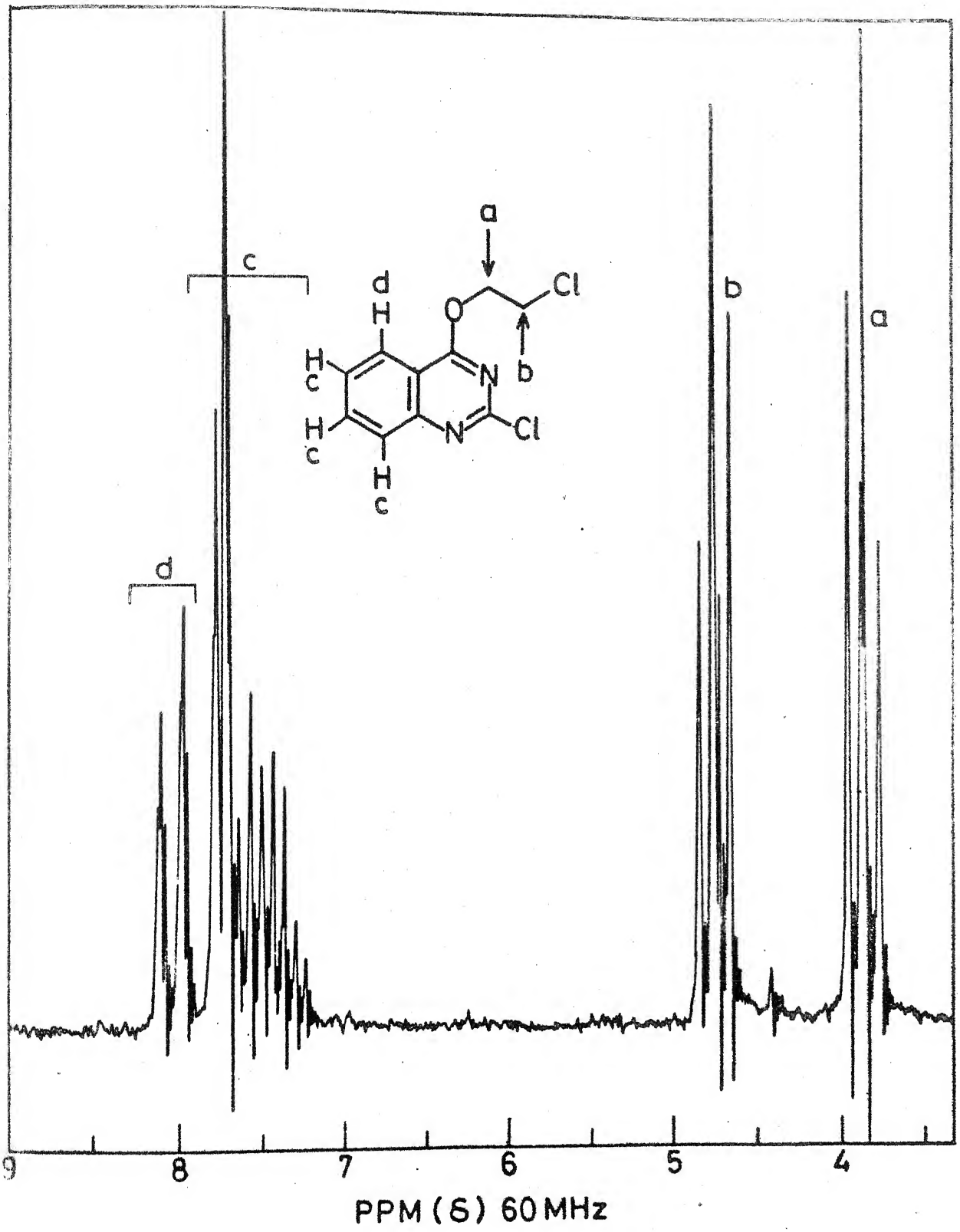

H
N
H
N
N
H
N
H
H
b
H
c
H
d
H
a
H
d
H
a
H
b
H
c
a
b
c
d
8
7
6
PPM (δ) 500 MHz

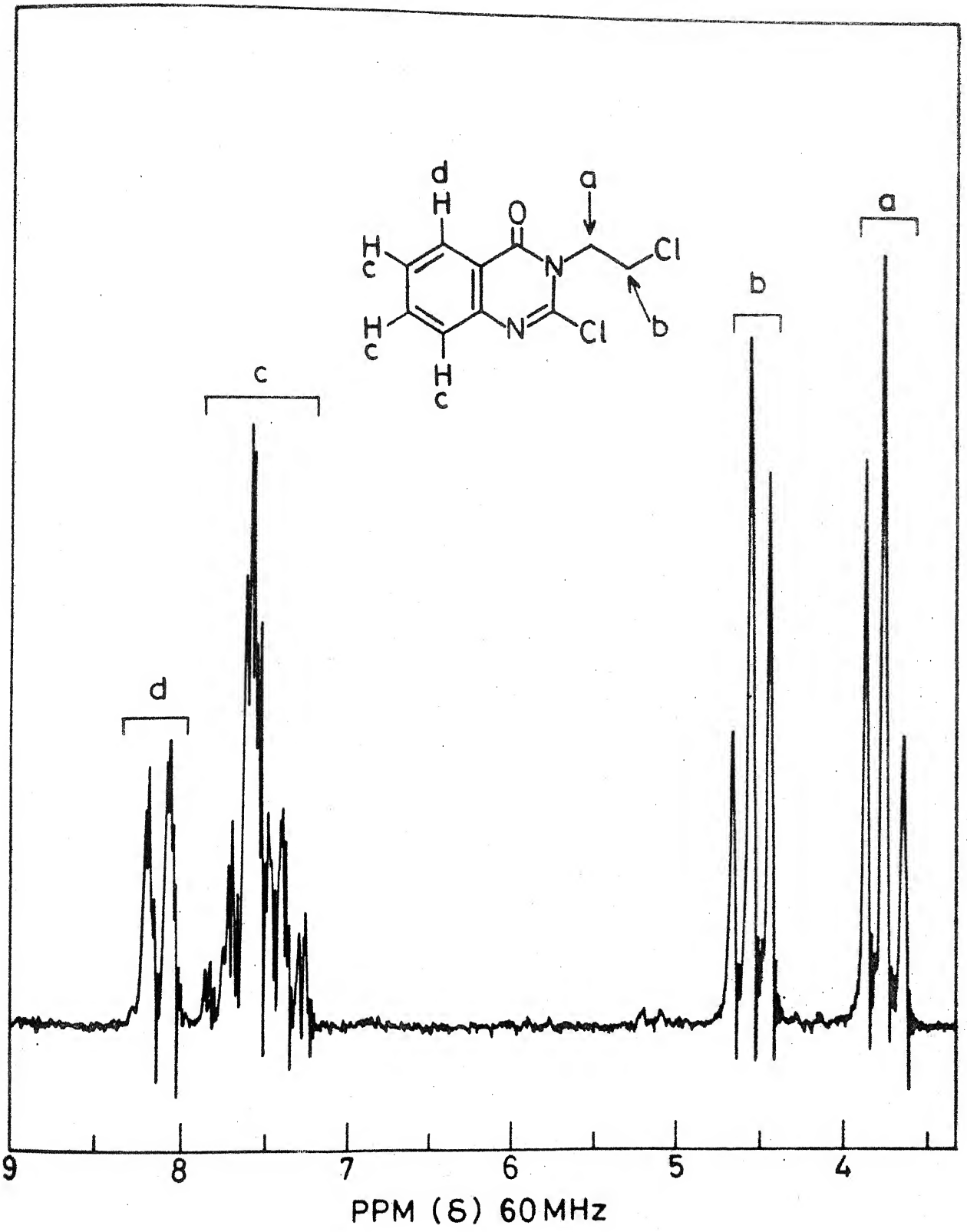

a
a
O
N
N
H
d
N
N
H
e
CH2
b
Ph
c
e
d
c
b
a
9
8
7
8
7
6
5
4
3
2
1
PPM (δ) 60 MHz

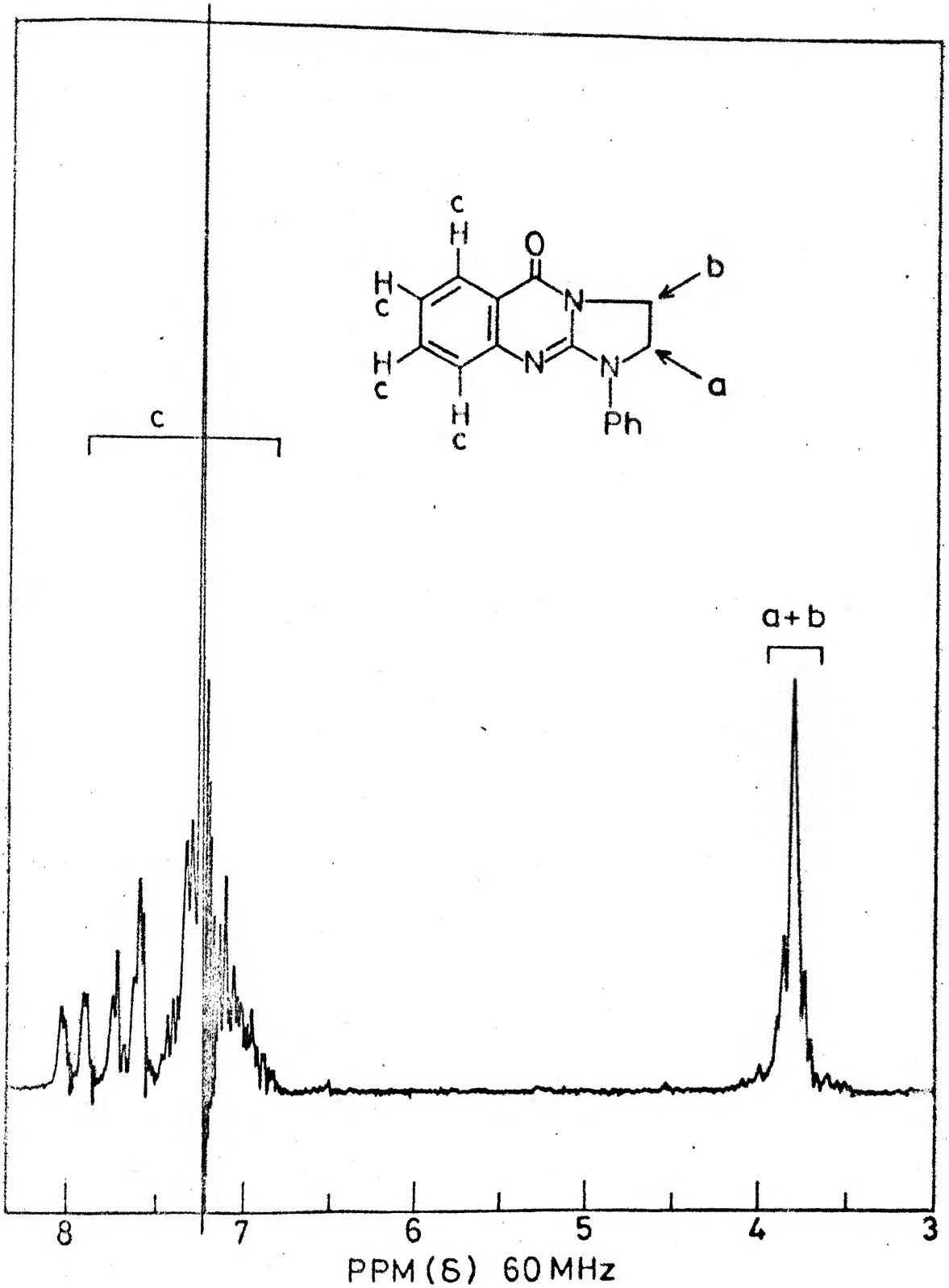

a
b
c
d
e
c
b
Ph
CH2
O
N
a
a
H
d
N
N
N
N
H
e
9
8
7
6
5
8
7
6
5
4
3
2
1
PPM (δ) 60MHz

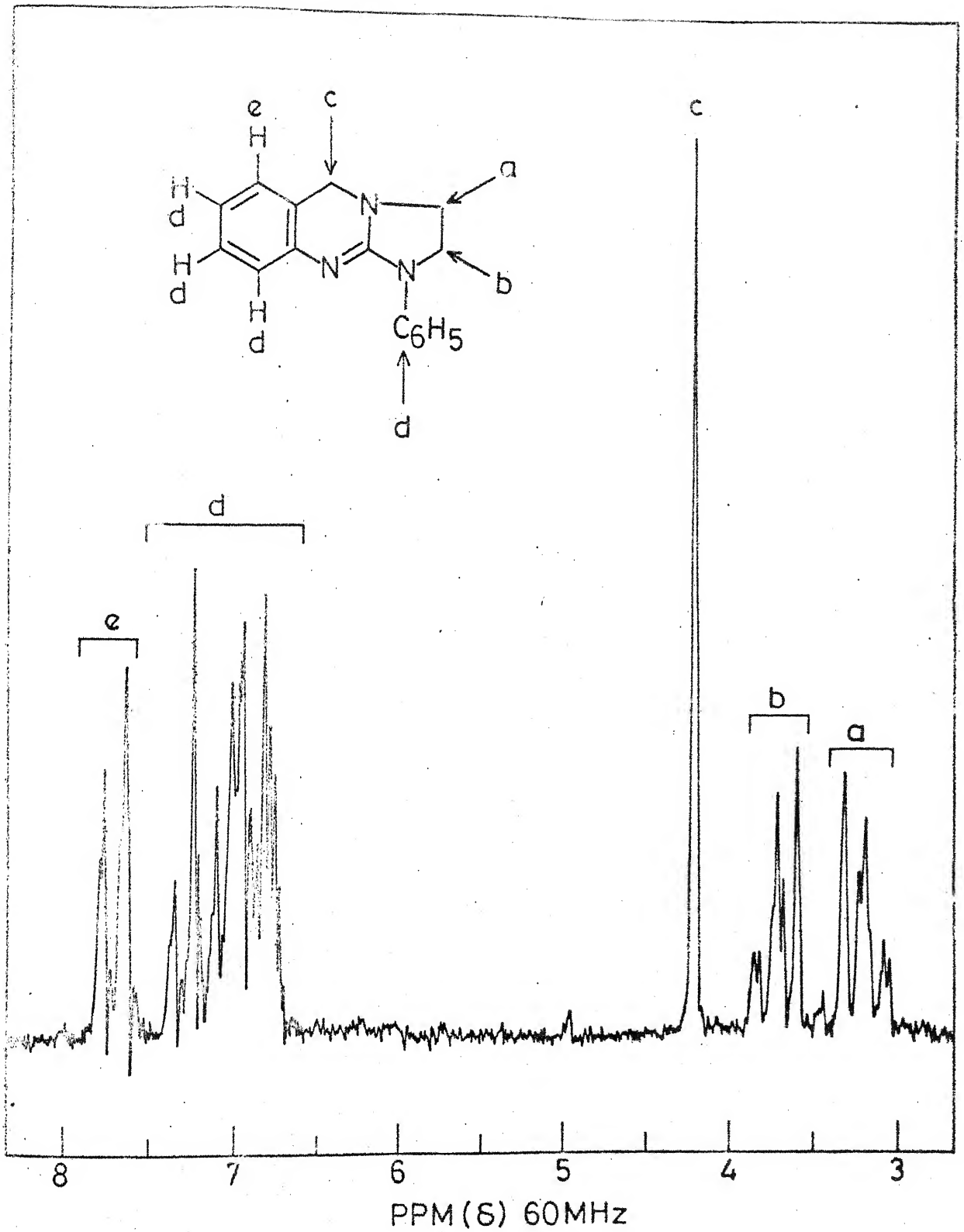

b
b
b
N
O
N
N
H
e
N
N
H
f
a
H
d
O
a
a
c
f
e
d
c
a
8
8
7
6
5
4
3
2
1
PPM (δ) 60 MHz

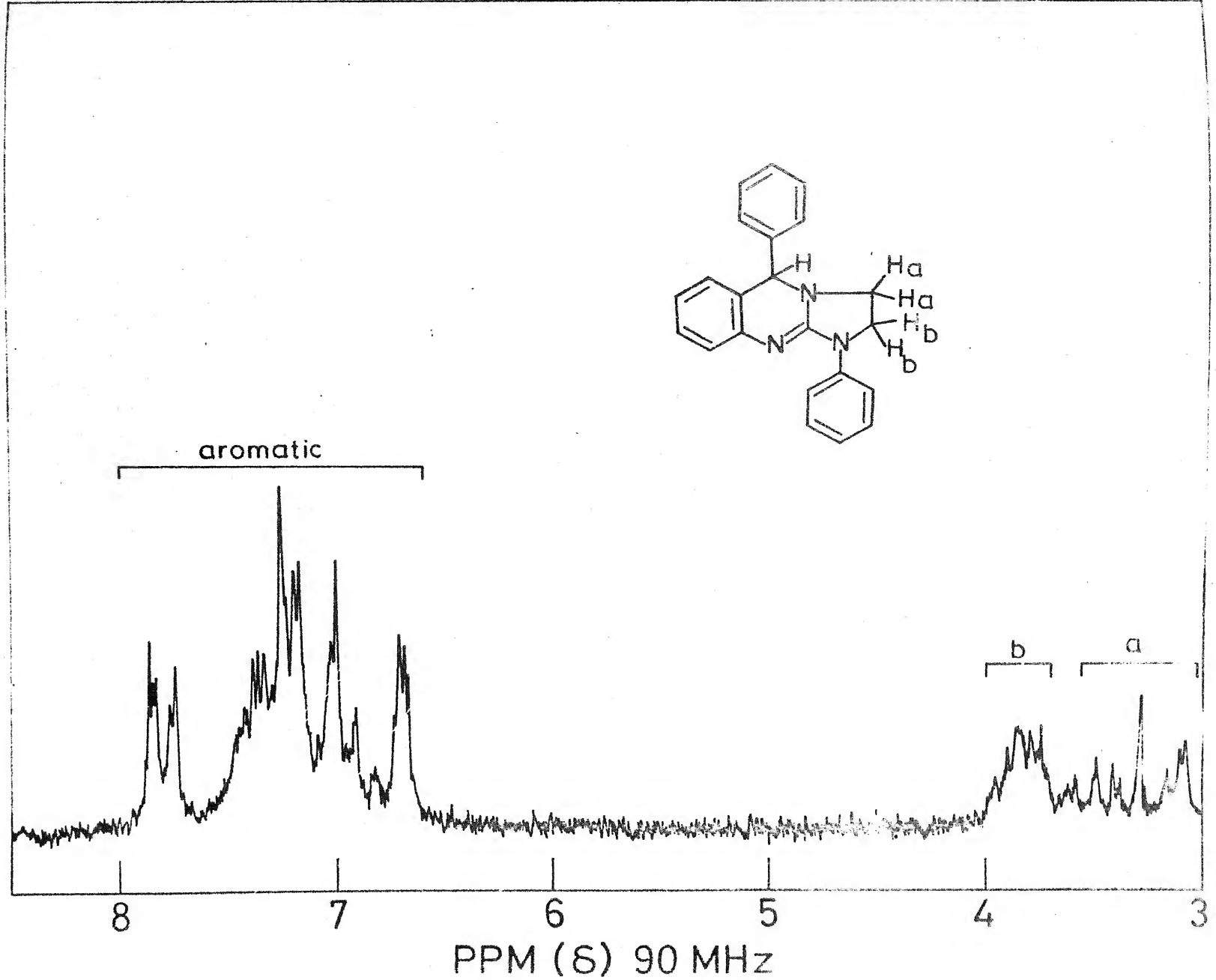

O
N
H
H
g
N
N
H
h
c
b
O
H
f
a
H
H
d
e
H2O in
DMSO
DMSO
g+h
f
d+e
a+b+c
9
8
7
6
5
4
3
2
PPM (δ) 200MHz

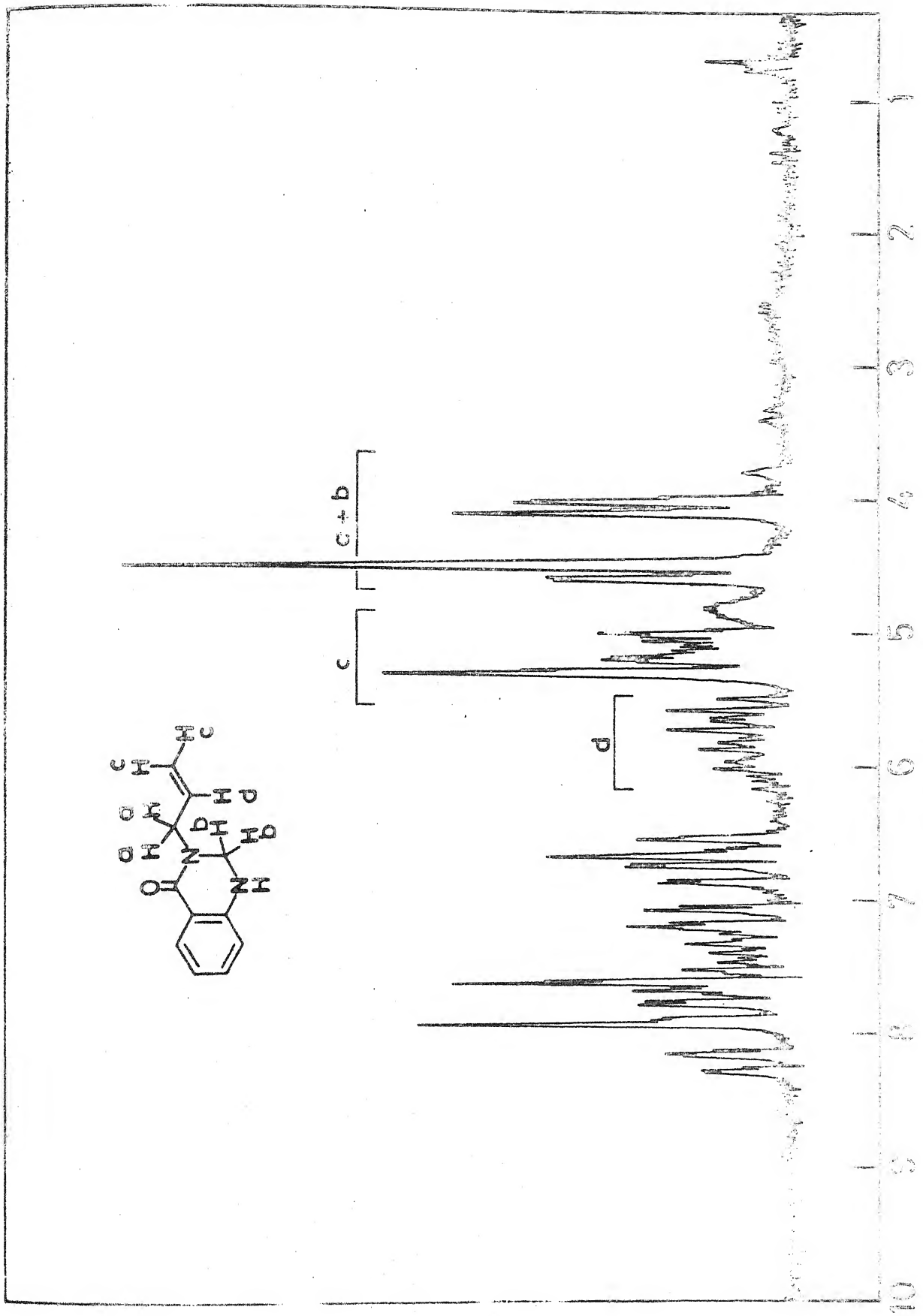

a
c
d
H
O
Cl
b
H
c
N
H
c
N
Cl
H
c
d
b
a
9
8
7
6
5
4
PPM (δ) 60 MHz

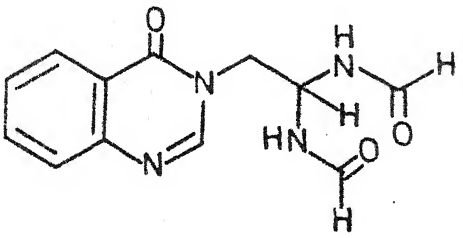

d
H
a
O
H
c
N
Cl
H
c
N
Cl
b
H
c
a
b
c
d
9
8
7
6
5
4
PPM (δ) 60 MHz

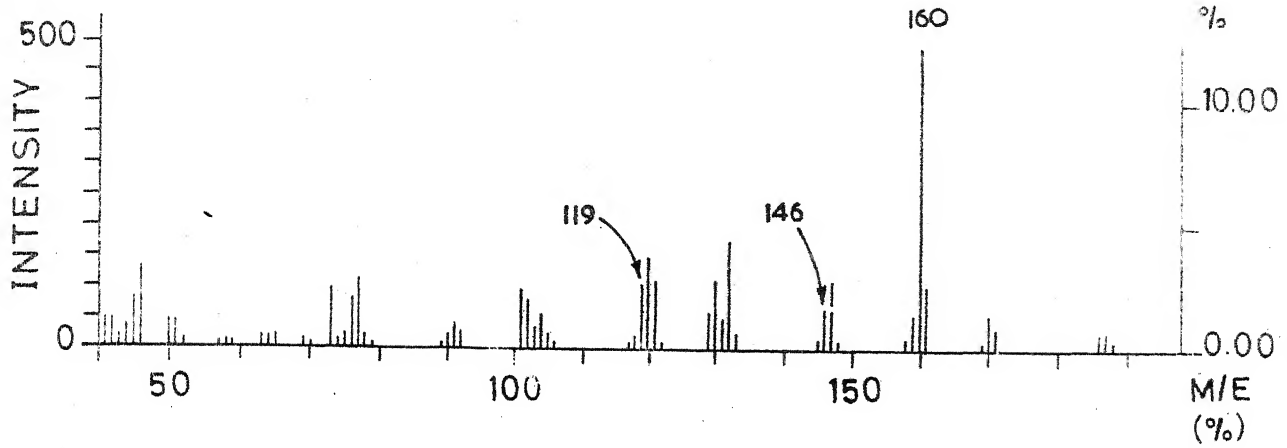

c
H
O
H
c
b
N
H
c
N
N
a
H
c
Ph
c
a+b
8
7
6
5
4
3
PPM (δ) 60 MHz

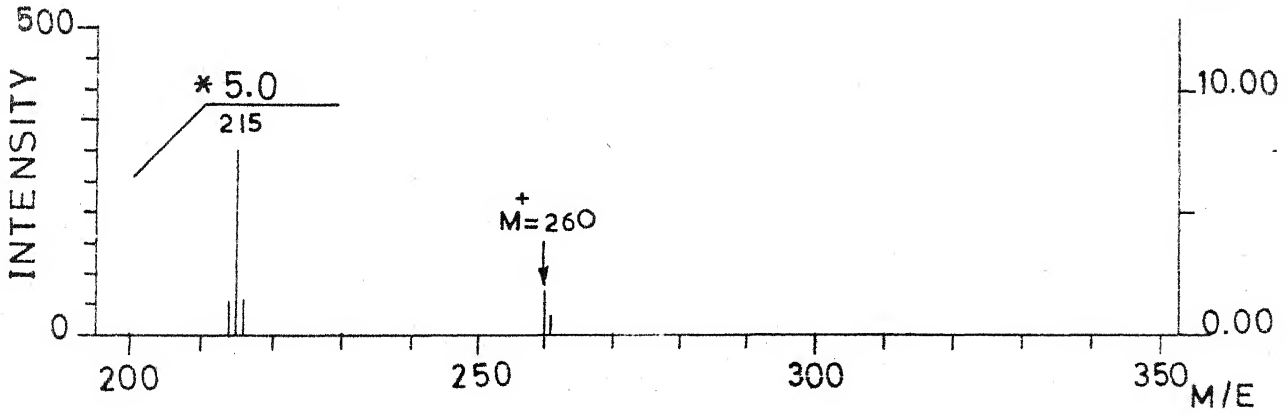

e
H
c
a
H
d
N
H
d
N
N
b
H
d
C6H5
d
c
d
e
b
a
8
7
6
5
4
3
PPM (δ) 60MHz

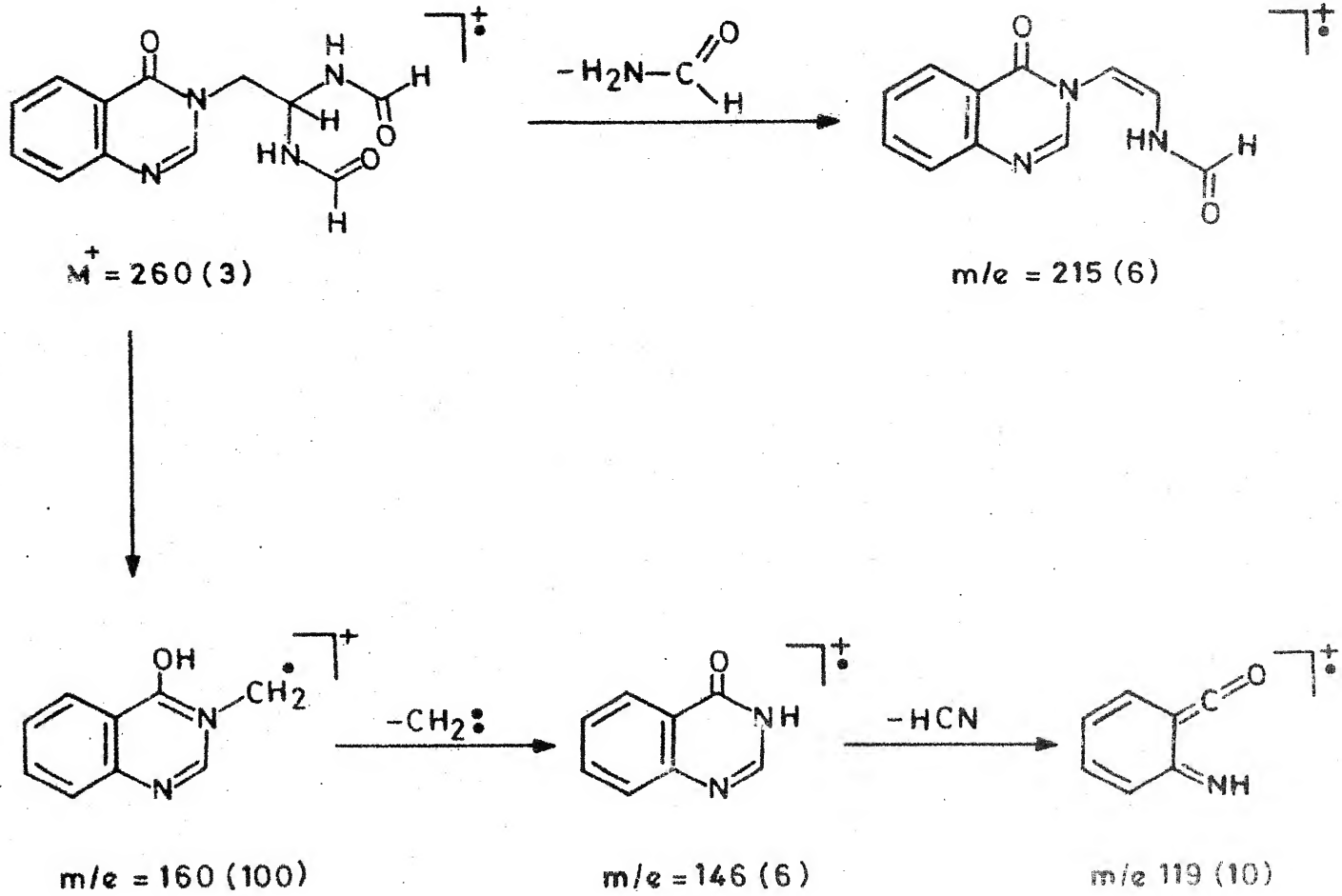

H
Ha
Ha
Hb
Hb
N
N
N
aromatic
b
a
8
7
6
5
4
3
PPM (δ) 90 MHz

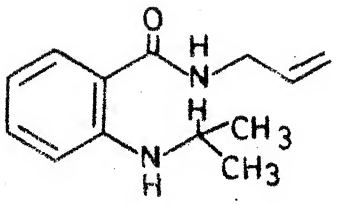

c + b
c
d
δ (ppm) 60MHz

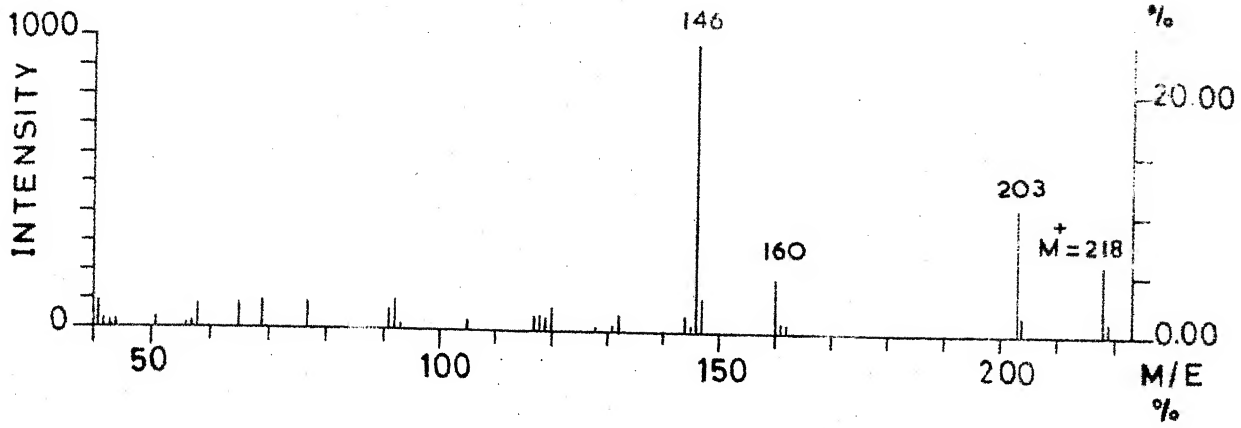

O
N
H
N
H
H
O
HN
O
H
N
H

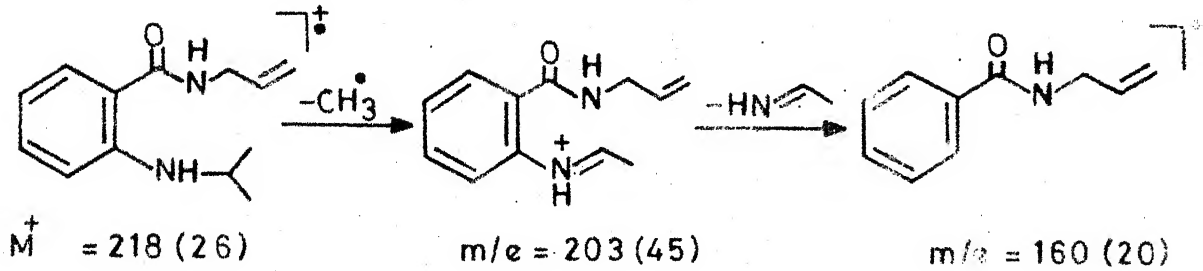

500
INTENSITY
0
160
%
10.00
119
146
0.00
50
100
150
M/E
(%)

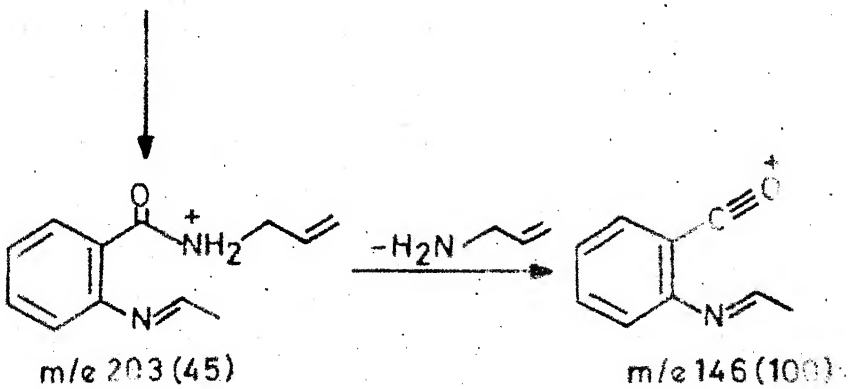

500
INTENSITY
0
* 5.0
215
+
M=260
10.00
0.00
200
250
300
350
M/E

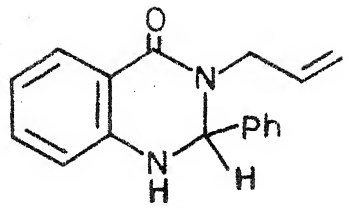

$-H_2N-C(=O)H$
$M^+ = 260\ (3)$
m/e = 215 (6)
$-CH_2:$
$-HCN$
m/e = 160 (100)
m/e = 146 (6)
m/e 119 (10)

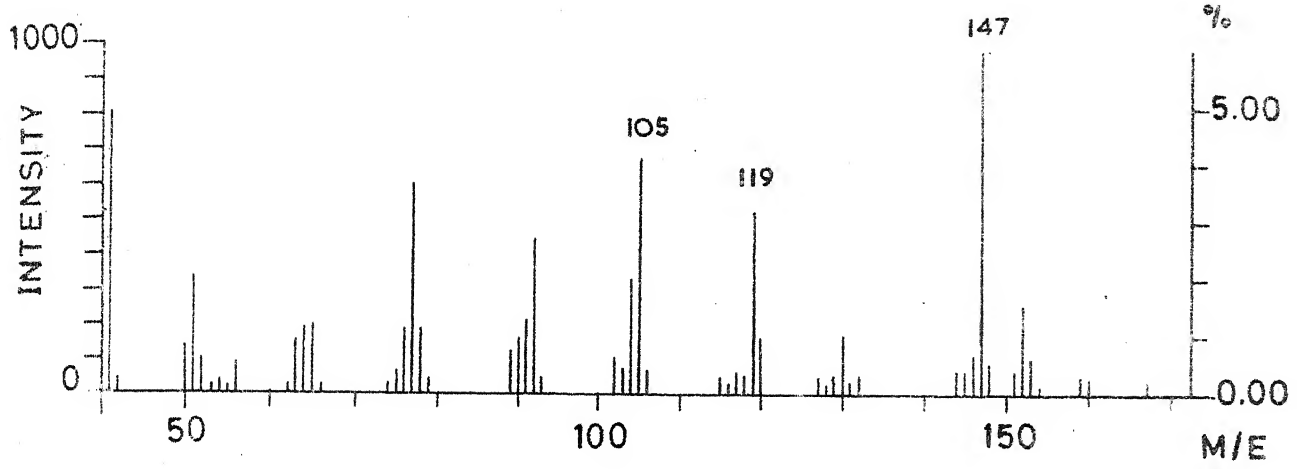


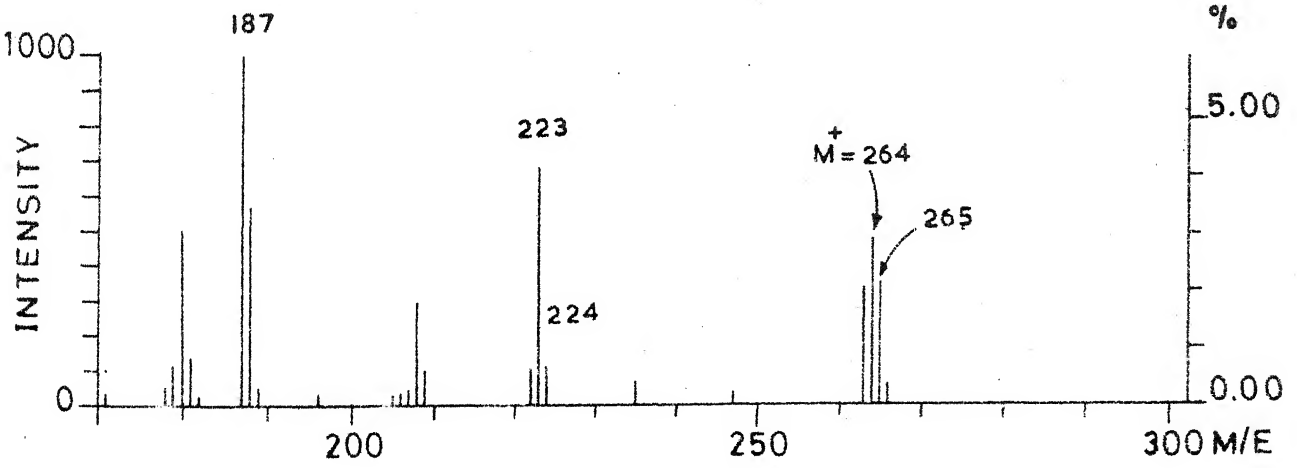

1000
INTENSITY
0
146
160
203
M+ = 218
%
20.00
0.00
50
100
150
200
M/E
%

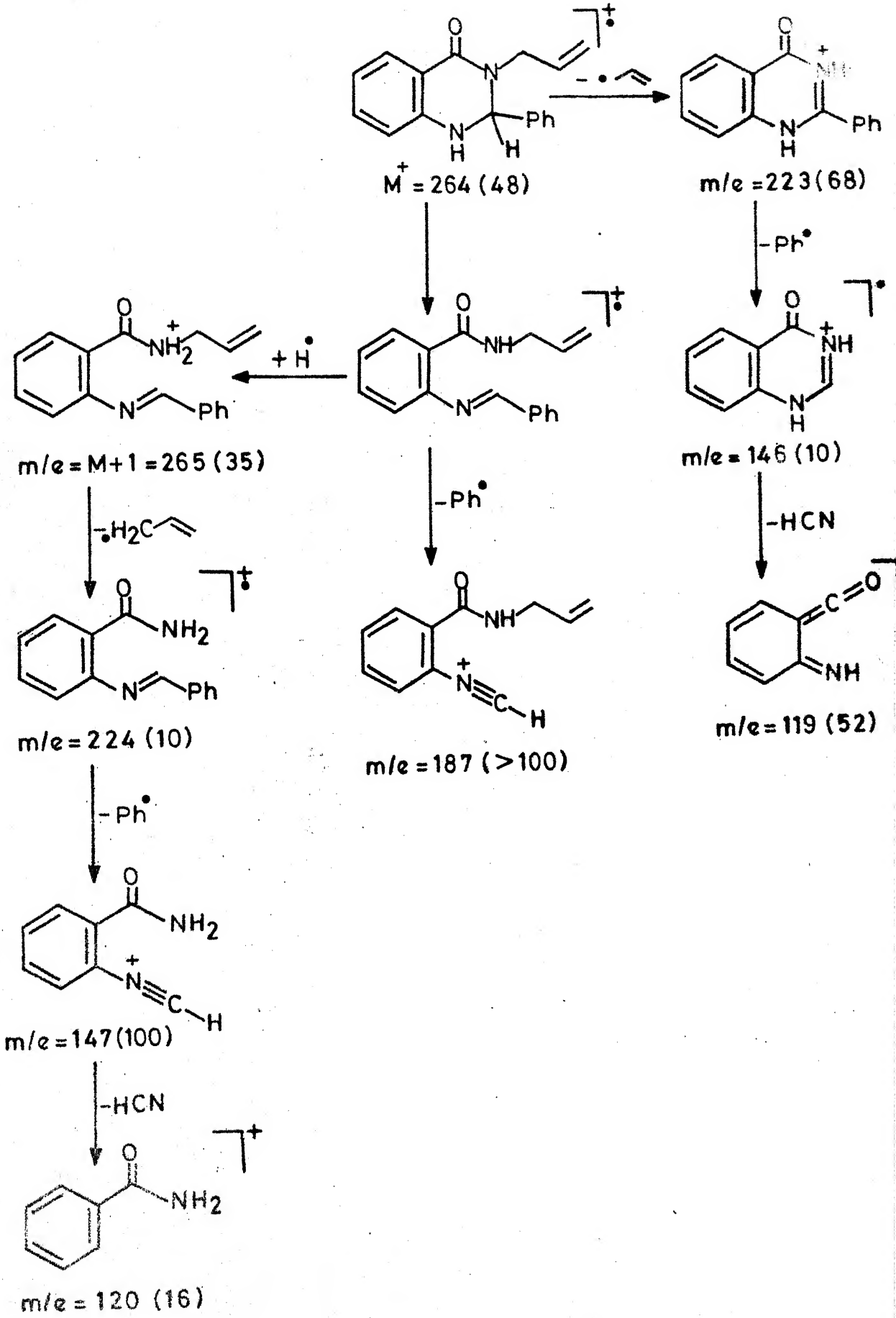

-CH3
-HN
M+ = 218 (26)
m/e = 203 (45)
m/e = 160 (20)

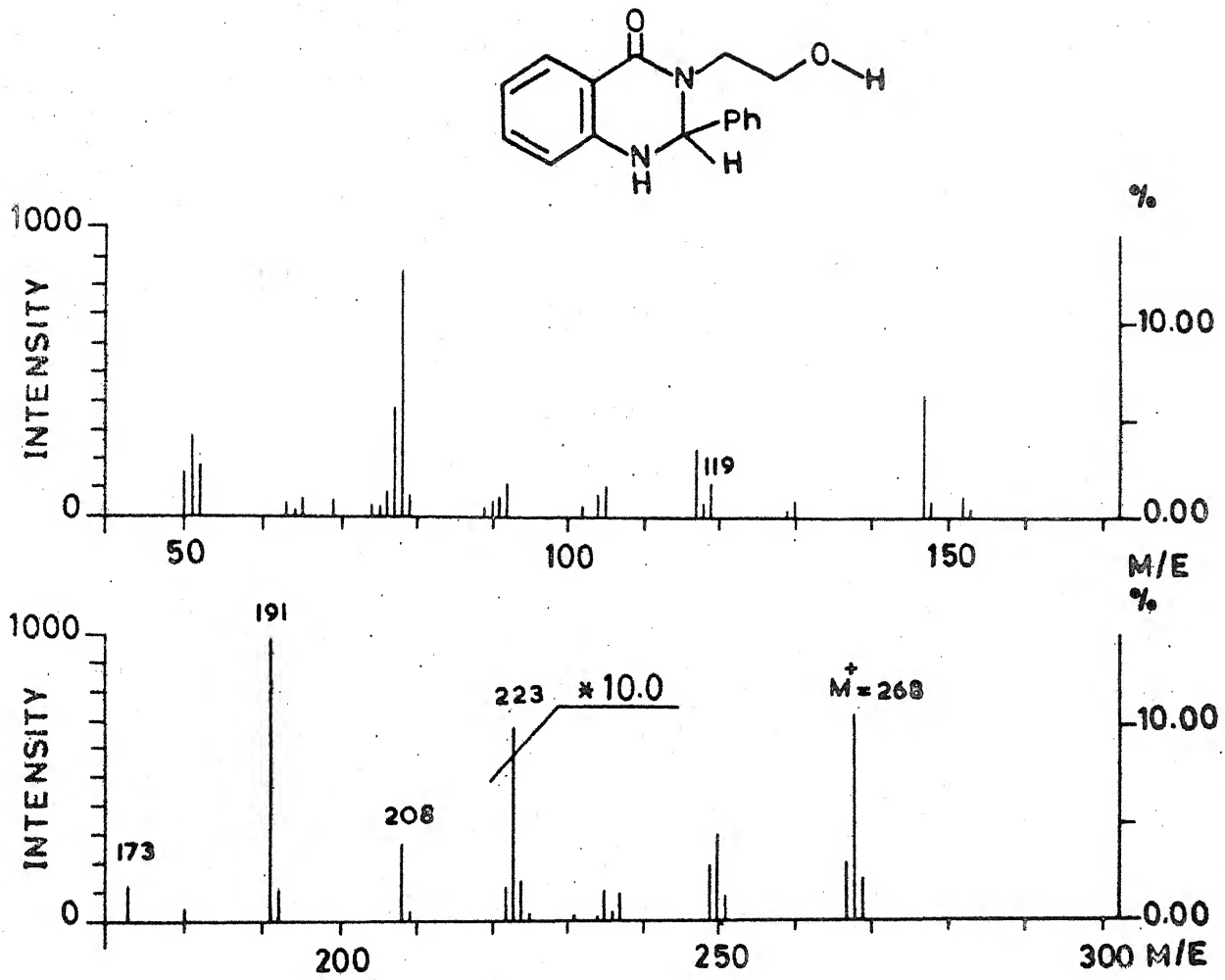

-H2N
m/e 203 (45)
m/e 146 (100)

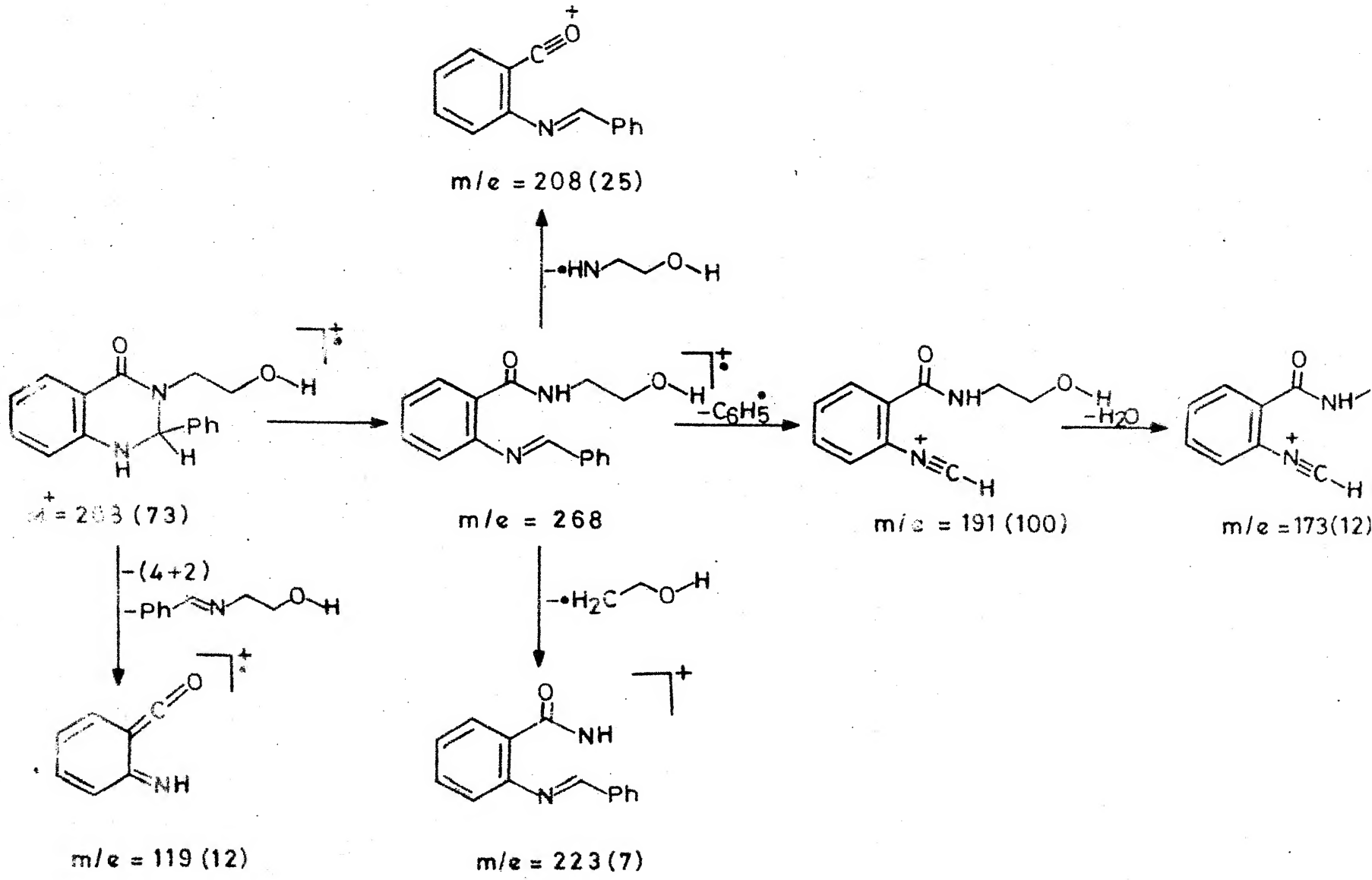

O
N
Ph
N
H
H

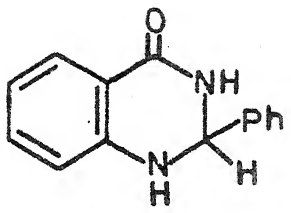

1000
INTENSITY
0
147
105
119
%
5.00
0.00
50
100
150
M/E

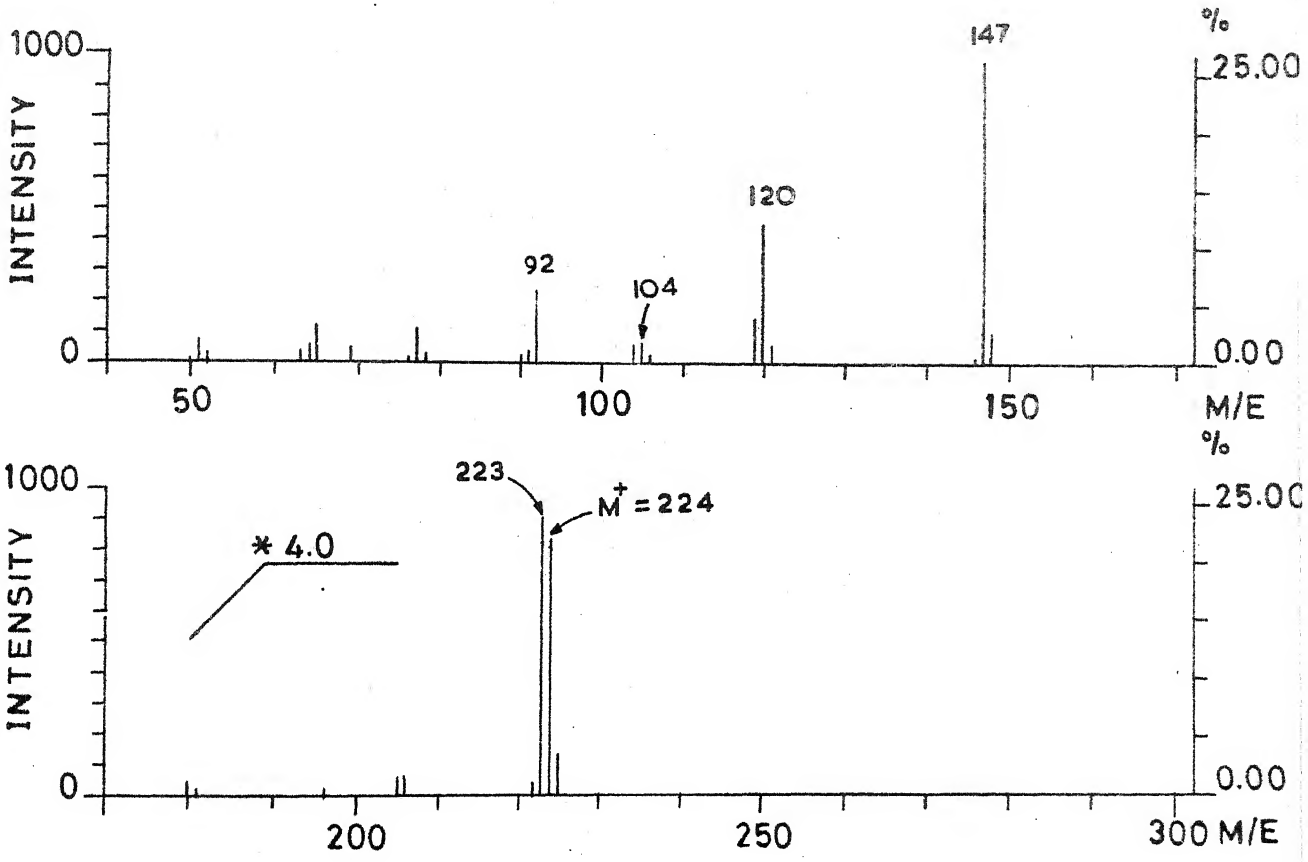

1000
INTENSITY
0
187
223
224
M = 264
265
%
5.00
0.00
200
250
300 M/E

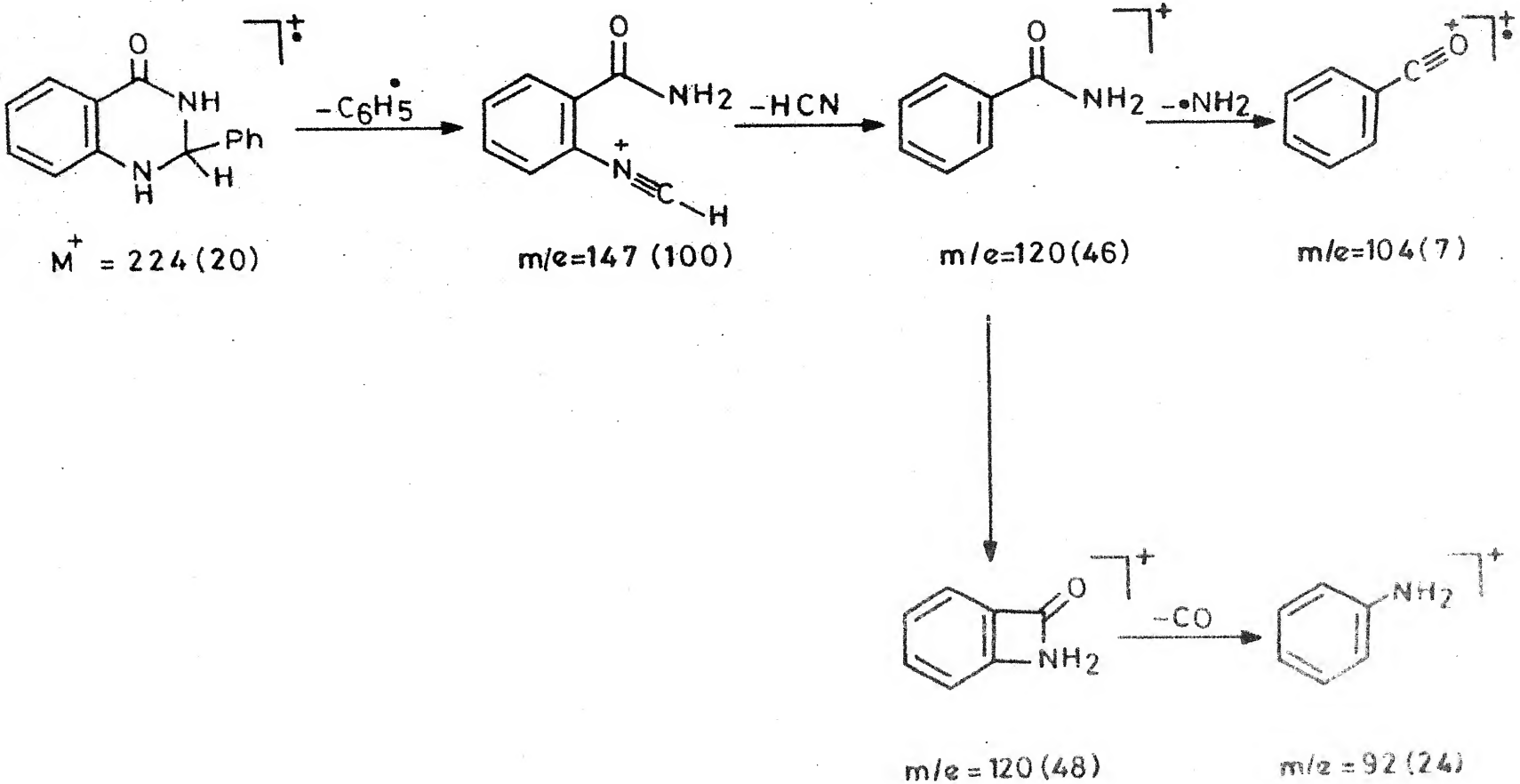

M+ = 264 (48)
m/e = 223 (68)
m/e = 146 (10)
m/e = 119 (52)
m/e = M+1 = 265 (35)
m/e = 187 (>100)
m/e = 224 (10)
m/e = 147 (100)
m/e = 120 (16)
-Ph•
-HCN
+ H•
-H2C=CH2

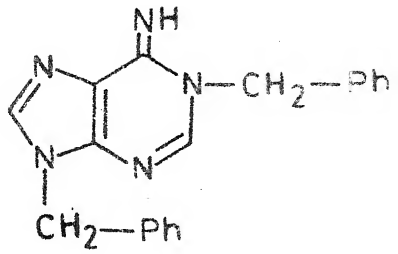

O
N
O
H
Ph
N
H
H
1000
INTENSITY
0
%
10.00
0.00
119
50
100
150
M/E
1000
INTENSITY
0
%
191
223
*10.0
M+=268
10.00
208
173
0.00
200
250
300 M/E

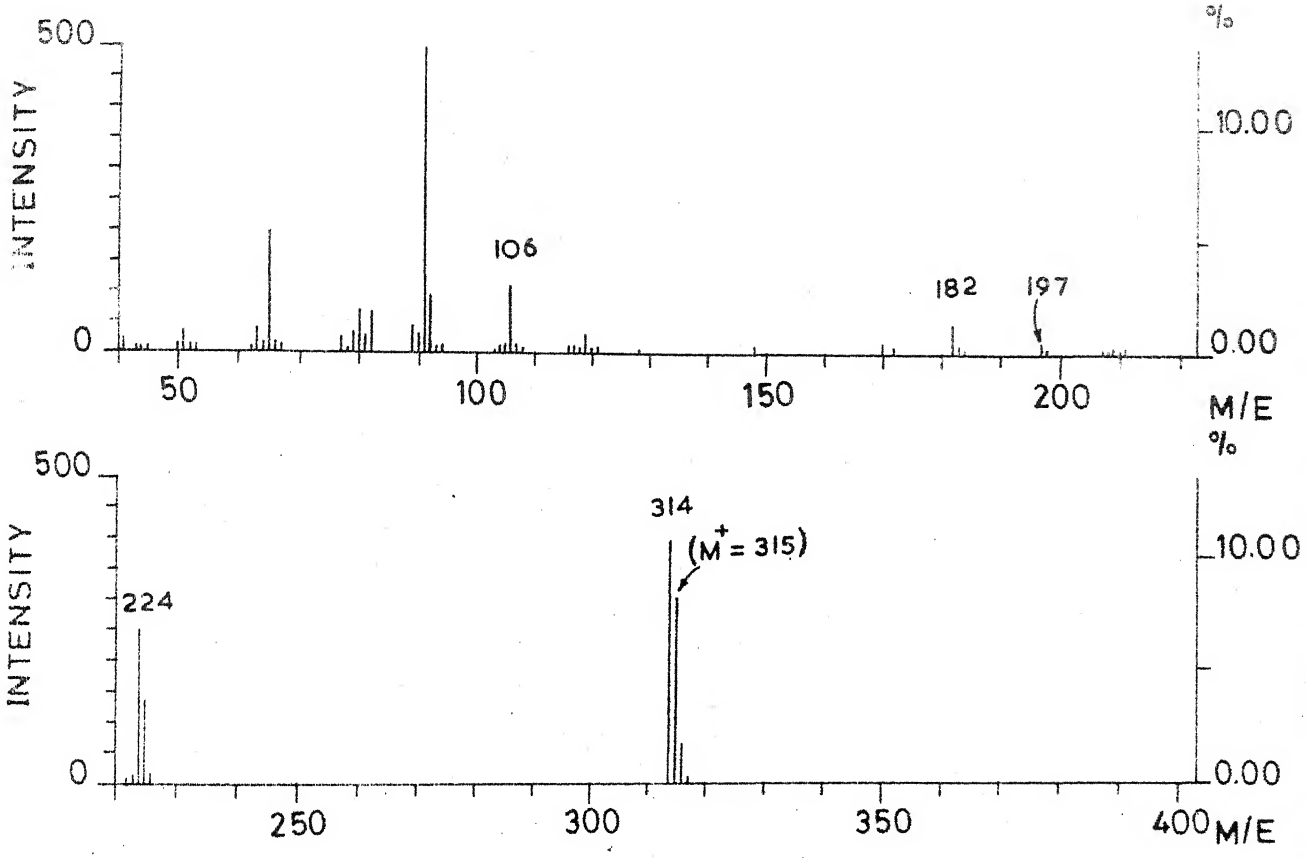

m/e = 208 (25)
-•HN
O
H
-(4+2)
-Ph
N
O
H
-•H2C
O
H
-C6H5•
-H2O
NH
Ph
m/e = 268
m/e = 191 (100)
m/e = 173(12)
m/e = 119 (12)
m/e = 223 (7)

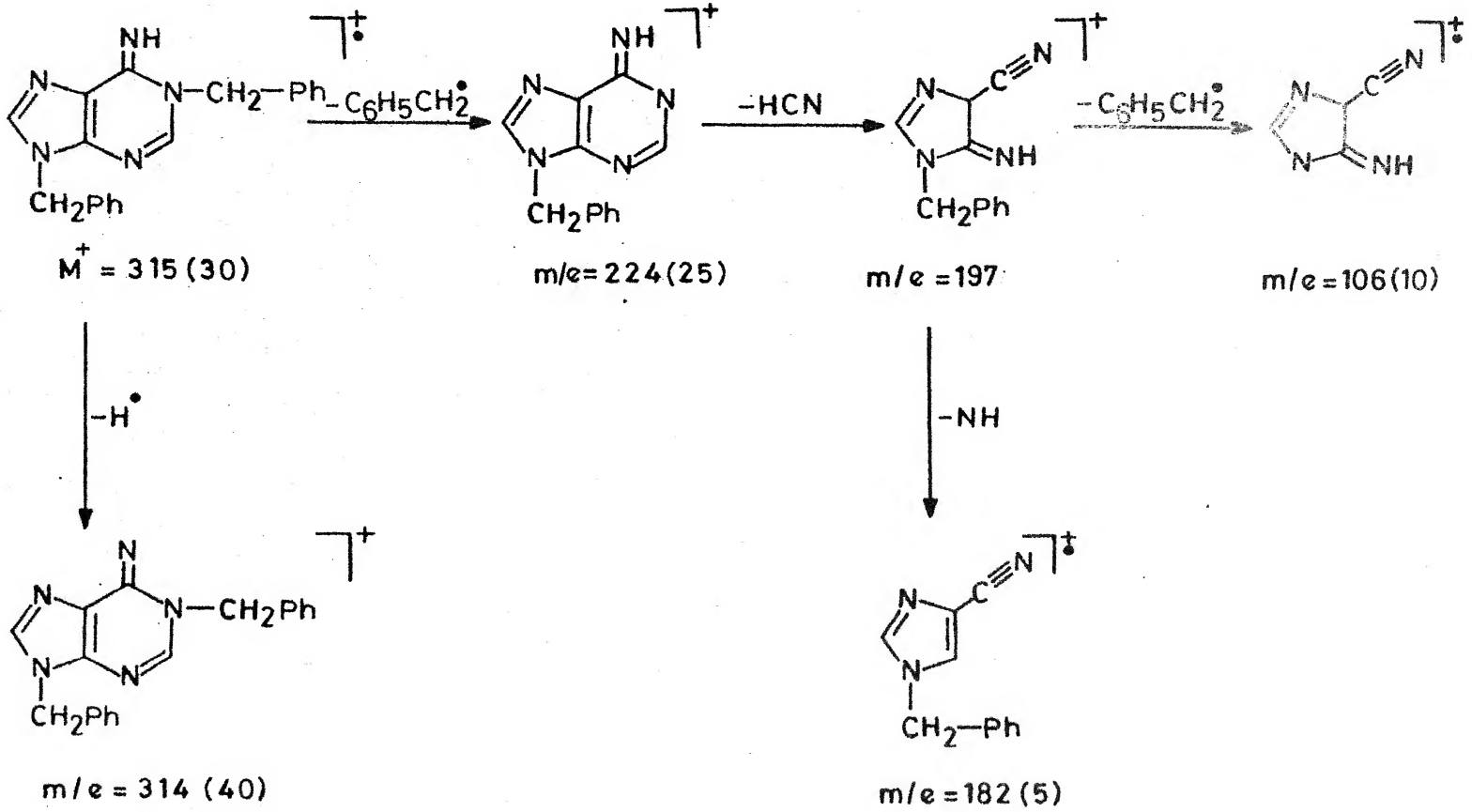

O
NH
Ph
N
H
H


1000
INTENSITY
0
%
25.00
0.00
147
120
92
104
50
100
150
M/E
1000
INTENSITY
0
223
M+ = 224
* 4.0
%
25.00
0.00
200
250
300 M/E


O
NH
Ph
N
H
H
M^+ = 224 (20)
$-C_6H_5^{\bullet}$
O
NH_2
N^+
C
H
m/e=147 (100)
-HCN
O
NH_2
m/e=120(46)
$-{}^{\bullet}NH_2$
O
C
O
m/e=104(7)
O
NH_2
m/e = 120 (48)
-CO
NH_2
m/e = 92 (24)


NH
N
N—CH2—Ph
N
N
CH2—Ph


500
INTENSITY
0
%
10.00
0.00
106
182
197
50
100
150
200
M/E
500
INTENSITY
0
%
10.00
0.00
224
314
(M+ = 315)
250
300
350
400
M/E


NH
N
N–CH2–Ph
CH2Ph
+•
–C6H5CH2•
–HCN
NH
CN
–C6H5CH2•
M+ = 315 (30)
m/e= 224 (25)
m/e =197
m/e =106 (10)
–H•
–NH
m/e = 314 (40)
m/e =182 (5)

E. EXPERIMENTAL

Melting points and boiling points are uncorrected. Infrared spectra were recorded on Perkin-Elmer, Model-377 and Perkin-Elmer Model-580 spectrophotometers as thin films for liquids and KBr discs for solids. NMR spectra were obtained on approximately 10-20% solutions in $CDCl_3$, and DMSO-d_6 on EM-360, XL-200, R-32, TR-90, R-600 and a 500 MHz instrument. The chemical shifts are reported in parts per million downfield from tetramethyl silane at 0.00 as internal standard. Silica gel G (ACME) was used for thin layer chromatography and column chromatography was done on silica gel (ACME, 100-200 mesh), columns were prepared from its slurry in petroleum ether (60°-80°C) and distilled benzene. Reactions were monitored, wherever possible, by tlc.

I. 3,4-Dihydro-4-oxo quinazoline[33] (2)

An intimate mixture of anthranilic acid 1 (54.8g, 0.426m) and formamide (26.8ml, 0.524m) was heated in an open beaker (250 ml) first at 135°C for 3 hr and then at 170-180°C for 2 hr. During the first phase of heating, evolution of ammonia was observed and towards the completion of 3 hr, the entire mass solidified to a cake. This was powdered, extracted with hot water (200 ml), filtered and the residue on crystallisation from hot water (750 ml) gave 50.2 g (85%) of 2, mp. 216°C (lit.[33] mp. 216°C).

ir : ν_{max}(KBr)(cm^{-1}): 3200, 3170 (amide NH), 1700 (amide carbonyl).

II. 6-Nitro-3,4-dihydro-4-oxoquinazoline[35] (3)

3,4-Dihydro-4-oxoquinazoline (2) (20.0 g, 0.137 m) was added in small portions to a nitrating mixture prepared from fuming nitric acid (40 ml) and concentrated sulphuric acid (40 ml cooling the reaction flask under the tap after each addition. The mixture was heated on a boiling water bath for 0.75 hr, cooled to 0°, poured over crushed ice (1.5 kg), the powdery, yellow product filtered, washed with chilled water (5 x 25 ml) air dried and then *in vacuo* to yield 23.73 g (90.8%) of 3, mp. 286°C (lit.[35] mp. 284°C).

ir : ν_{max}(KBr)(cm^{-1}): 1675 (amide carbonyl), 1610, 1575 (C=C, C=N), 1510, 1350 (nitro).

III. 4-Chloroquinazoline[34](4)

Under protection from moisture, a mixture of 2 (18.0 g, 0.123 m), PCl_5 (34.5 g, 0.166 m) and $POCl_3$ (144 ml, 1.55 m) was refluxed for 2 hr. The $POCl_3$ was removed from the resulting clear solution at 35-40 mm, the residue admixed with chloroform (150 ml), poured slowly over crushed ice (300 g), adjusted under ice cooling to pH 8 with aqueous ammonia (sp. gr. 0.89), the organic layer was separated, the aqueous layer extracted with additional chloroform (2 x 50 ml), the combined extracts dried ($MgSO_4$), evaporated at 15 mm and the residue was extracted with benzene. The benzene extract was passed through a column of basic alumina and then through a bed of charcoal (BDH) and evaporation of solvents at 15 mm gave 4-chloroquinazoline (4) as a white crystalline solid, mp. 97°C (lit.[34] mp. 97°C), yield 15.0 g (74%).

IV. 4-Allyloxyquinazoline (5)

Under protection from moisture and stirring, sodium (0.2 g, 8.7 mmol) was added to excess allyl alcohol (10.0 ml) followed by, after completion of the reaction, 4-chloroquinazoline 4 (1.2 g, 7.2 mmol). The reaction mixture was refluxed for 3 hr, solvents

evaporated *in vacuo*, triturated with benzene, decanted, evaporat and the resulting viscous oil distilled to give 1.2 g (80%) of 5 bp. 130°C/0.2 mm.

tlc : PhH:EtOAc:: 97:3; Rf. 0.35.

Anal.Calcd for $C_{11}H_{10}N_2O$ (Mol. Wt. 186)

C, 70.96; H, 5.37; N, 15.05%

Found C, 71.0 ; H, 5.21; H, 15.4 %

ir : ν_{max}(neat) cm^{-1}: 3070, 3040 (aromatic, olefinic C-H), 1620, 1570 (C=C, C=N), 1090 (ether).

nmr: $\delta(CDCl_3)$ 60 MHz: 5.0 (m , 2H, O-CH_2-CH), 5.2 (m, 2H, -CH=CH_2), 6.1 (m, 1H, -CH=CH_2), 7.25-8.5 (m, 4H, benzene ring), 8.66 (s, 1H, pyrimidine ring).

V. Claisen Rearrangement of 5: Isolation of 3-Allyl-3,4-dihydro-4-oxoquinazoline (6)

4-Allyloxyquinazoline (1.0 g, 53.7 m mol) was sealed unde nitrogen in a pyrex tube and held at 200°C for 24 hr. The dark brown pyrolysis product was separated from small amounts of 2, which had sublimed, triturated with CH_2Cl_2, evaporated and the residue chromatographed on silica gel. Elution with benzene: ethyl acetate::4:1 gave 5, which was distilled (bp. 135°C/0.15 m The distillate solidified to a crystalline mass of pure 6, mp.65 (lit. 65°C), yield 0.75 g (75%).

Anal. Calcd for $C_{11}H_{10}N_2O$ (Mol. Wt. 186)

C, 70.96; H, 5.37%

Found C, 71.06; H, 5.33%

ir : ν_{max}(KBr) cm^{-1}: 1675 (amide carbonyl), 1615, 1570 (C=C, C=N).

nmr: δ($CDCl_3$) 60 MHz: 4.55 (m, 2H, N-$C\underline{H}_2$-CH), 5.18 (m, 2H, -CH=$C\underline{H}_2$), 5.88 (m, 1H, -$C\underline{H}$=CH_2), 7.2-7.7 (m, 3H, 6',7',8'-quinazoline ring), 7.9 (s, 1H, 2'-quinazoline ring), 8.1 (m, 1H, 5'-quinazoline ring)

VI. Reaction of 2 with Allylbromide: Direct preparation of 6

Under stirring freshly distilled allyl bromide (1.3 g, 10 m mol) was added to a clear solution of the potassium salt of 2-prepared from 2 (1.2 g, 6.5 m mol) and KOH pellets (0.5 g, 9 m mol) in dry methanol (20 ml). The alkylation was complete after 2 hr reflux (tlc:PhH;EtOAc::97:3; Rf. 0.2). Solvents were evaporated *in vacuo*, the residue triturated with dry benzene, passed through a column of basic alumina, evaporated and crystallised from hot petroleum ether to give 1.3 g (85%) of 6, mp. 65°C.

VII. Reaction of 6 with Sodium aluminium chloride: Isolation of 2 by fragmentation:

Preparation of sodium aluminium chloride:

An intimate mixture of sodium chloride (BDH, AR, 5.85 g, 100 m mol) and anhydrous aluminium chloride (BDH, 26.66 g, 200 m mol) was brought to a melt over a flame. The clear homogeneous mixture that resulted was cooled, powdered and stored dry.

Attempted cyclisation of 6 with $NaAlCl_4$:

A mixture of 3-Allyl-3,4-dihydro-4-oxoquinazoline 6 (1.0 g, 54 m mol) and excess $NaAlCl_4$ (10.0 g) was held at 210°C for 2 hr, cooled, powdered and dissolved in ice cold water (~ 200 ml) extracted with EtOAc and solvents evaporated to give 0.745 g (95%) 2, mp. 216°C.

VIII. Osmium tetroxide-periodate degradation of 6: Isolation of aldehyde 7

Under stirring and protection from light, OsO_4 (0.065 g, 2.5 m mol) was added to a solution of 6 (1.0 g, 5.4 m mol) in dry dioxane (20 ml). The reaction mixture was left stirred for 0.75 hr and the resulting brown solution was admixed with, in drops, over 2.5 hr, a solution of $NaIO_4$ (BDH, AR, 2.25 g, 18 m m in distilled water (20 ml), left stirred overnight, filtered,

washed with ether, ethyl acetate, the combined filtrates evaporated *in vacuo*, the residue dissolved in water, extracted with ethyl acetate, dried ($MgSO_4$), and evaporated to give 0.4 g (40%) of 3-(2'-Oxoethyl)-3,4-dihydro-4-oxoquinazoline 7, mp. 152°C, which was identical with the aldehyde obtained by the hydrolysis of 3-(2'-Diethoxyethyl)-3,4-dihydro-4-oxoquinazoline 8 (vide infra).

IX. Alkylation of 2 with 2-Bromo-1,1-diethoxyethane: Preparation of 3-(2'-Diethoxyethyl)-3,4-dihydro-4-oxoquinazoline (8)

3,4-Dihydro-4-oxoquinazoline 2 (2.0 g, 13.3 m mol) was introduced to a solution of sodium methoxide - prepared from sodium (0.32 g, 13.6 m mol) and methanol (15 ml). The mixture was left stirred for 1 hr resulting in a clear solution. Solvents were evaporated, the residue admixed with dry HMPA (10 ml), warmed to achieve a clear solution, admixed with 2-bromo-1,1-diethoxy ethane (Fluka, 2 ml, 1.52 g, 13.6 m mol) and left stirred at 100-120°C for 24 hr. The reaction mixture was cooled, poured over water (~ 300 ml) extracted with hexane (3 x 150 ml), washed with water, dried ($MgSO_4$) and solvents evaporated to give 2.25 g (63%) of 3-(2'-Diethoxyethyl)-3,4-dihydro-4-oxoquinazoline (8) mp. 79°C.

tlc: EtOAc; Rf. 0.8.

Anal. Calcd for $C_{14}H_{18}N_2O_3$ (Mol. Wt. 262).

C, 64.18; H, 6.87%

Found C, 64.02; H, 6.45%

ir : ν_{max}(KBr) cm^{-1}: 1680 (amide carbonyl), 1615, 1565 (C=C, C=N).

nmr: $\delta(CDCl_3)$90 MHz: 1.15 (t, 6H, CH_2-$\underline{CH}_3$), 3.58 (m, 4H, $\underline{CH}_2$-CH_3), 4.0 (d, 2H, -$\underline{CH}_2$-CH-), 4.65 (t, 1H, -CH_2-$\underline{CH}$-), 7.1-7.7 (m, 3H, 6',7',8'-quinazoline ring), 7.95 (s, 1H, 2'-quinazoline ring), 8.15 (d, 1H, 5'-quinazoline ring).

X. Hydrolysis of ketal 8: Isolation of aldehyde 7:

A stirred suspension of finely powdered acetal 8 (3.0 g, 11.4 m mol) was gradually heated to 80-90°C. The resulting light brown clear solution was cooled, poured over crushed ice (100 g), neutralised to pH 7-7.5, saturated with sodium chloride, extracted with ethyl acetate (3 x 150 ml), the extract passed through a short column of silicagel, dried ($MgSO_4$) and evaporated *in vacuo* to give 1.6 g (74.4%) of 7 as a white powder, mp. 152°C, whose properties were identical to the sample obtained by the OsO_4-$NaIO_4$ oxidation of the N-allyl compound 6. (vide supra)

Anal. Calcd. for $C_{10}H_8N_2O_2$ (Mol. Wt. 188).

C, 63.83; H, 4.25; N, 14.89%

Found C, 63.88; H, 4.65; N, 14.7 %

ir ir : ν_{max}(KBr) cm^{-1}: 1720 (aldehyde), 1675 (amide carbonyl)

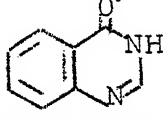
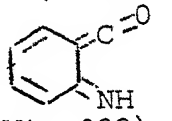
nmr: δ(DMSO-D_6) 500 MHz: 6.15 (d, 2H, N-$C\underline{H}_2$-CH), 7.52 (t, 1H, 6'-quinazoline ring), 7.66 (d, 1H, 8'-quinazoline ring), 7.8 (t, 1H, 7'-quinazoline ring), 8.15 (d, 1H, 5'-quinazoline ring), 8.22 (s, 1H, 2'-quinazoline ring).

XI. Reaction of aldehyde 7 with Hydroxylamine: Preparation of oxime 10

A solution of the aldehyde 7 (0.05 g, 0.27 m mol) in 95% ethanol (5 ml) was admixed with the hydroxylamine reagent solution - prepared from mixing of saturated aqueous solutions of hydroxylamine hydrochloride (0.027 g, 0.4 m mol) and NaOAc (0.048 g, 0.54 m mol), the mixture refluxed for 0.5 hr, solvents evaporated, the residue triturated with cold water, filtered, washed with cold water and dried to give, 0.24 g (44.4%) of oxime 10, mp. 163-64°C, whose properties were identical to that prepared directly from acetal 8 (vide infra).

XII. Reaction of ketal 8 with Hydroxylamine hydrochloride: Direct preparation of oxime 10

A solution of the ketal 8 (1.0 g, 3.8 m mol) in ethanol (10 ml) was admixed with an aqueous solution of hydroxylamine hydrochloride (0.53 g, 7.6 m mol, 10 ml) and the stirred mixture refluxed for 5 hr during which 8 was consumed (tlc). The reaction mixture was concentrated to ~ 7 ml, cooled, filtered, washed with small amounts of ice-cold water (3 x 10 ml) dried and recrystallised from hot EtOAc to give 0.55 g (71.4%) of the oxime 10, mp. 163-64°C.

Mass: m/e: 203 (M^+), 186 (M^+ - OH), 159 (M^+ -.HC=N-OH), 146 ()$^+$, 119 ()$^+$.

Anal. Calcd for $C_{10}H_9N_3O_2$ (Mol. Wt. 203).

C, 59.11; H, 4.43

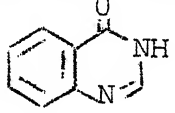
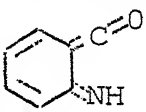
Found C, 59.13; H, 4.05

ir : ν_{max}(KBr) cm^{-1}: 1680 (amide carbonyl), 1615, 1515 (C=C, C=N).

nmr: δ(DMSO-d_6) 200 MHz: 4.75 (d,d, 2H, N-C$\underline{H}_2$), 6.88, 7.5 (t, t, 1H, C$\underline{H}$=N-OH), 7.5 (m, 1H, 6'-quinazoline ring), 7.65 (d, 1H, 8'-quinazoline ring), 7.8 (t, 1H, 7'-quinazoline ring), 8.15 (d, 1H, 5'-quinazoline ring), 8.35 (d, 1H, 2'-quinazoline ring), 11.0, 11.35 (s,s, 1H, =N-O$\underline{H}$).

XIII. Attempted Schiff base formation of aldehyde 9: Isolation of aminal 11

Under stirring and set-up for the removal of the water formed in the reaction, dry ammonia was passed through a refluxing suspension of the aldehyde 7 (0.463 g, 2.46 m mole) in dry benzene (100 ml) for 1.5 hr, cooled, filtered, washed with drybenzene and dried to give 0.41 g (82%) of 11, mp. 177°C.

Mass: m/e: 188 ($M^+ - NH_3$), 159 ($M^+ - \cdot CH(OH)NH_2$), 146 (), 119 ().

Anal. Calcd. for $C_{10}H_{11}N_3O_2$ (Mol. Wt. 205).

C, 58.54; H, 5.37%

Found C, 58.06; H, 5.37%

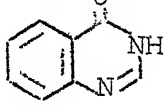
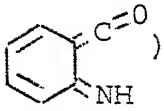
ir : ν_{max}(KBr) cm^{-1}: 3450 (OH), 3280, 3240 (NH_2), 1675 (amide carbonyl), 1610, 1565 (C=C, C=N).

nmr: δ(DMSO-d_6) 200 MHz: 3.85 (m, 3H, CH_2-CH-), 7.45 (d, 1H, 6'-quinazoline ring), 7.5 (d, 1H, 8'-quinazoline ring), 7.7 (m, 1H, 7'-quinazoline ring), 8.05 (d, 1H, 5'-quinazoline ring), 8.1 (s, 1H, 2'-quinasoline ring).

XIV. Reaction of acetal 8 with Formamide: Formation of the bis-formimino compound 12

A solution of the ketal 8 (1.048 g, 4 m mol) in formamide

(0.603 g, 0.54 ml, 13.7 m mol) was refluxed for 24 hr, the dark brown supernatant liquid removed by suction from the crystalline mass, washed with dry benzene, dry CH_2Cl_2 and crystallised from methanol to give 0.22 g (36.6%) of 12, mp.254°C

Mass: m/e: 260(M^+), 215 (M^+ - H_2N-CHO), 160(M^+-.$CH(CONH_2)_2$) 146 ()$^+$, 119 ()$^+$.

Anal. Calcd. for $C_{12}H_{12}N_4O_3$ (Mol. Wt. 260).

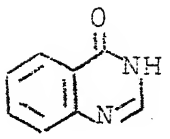
C, 55.38; H, 4.64%

Found C, 55.65; H, 4.48%

ir : ν_{max}(KBr) cm^{-1}: 3310 (N-H), 1670 (br, formyl and ring amides), 1610, 1540 (C=C, C=N).

XV. Attempted Schiff base formation of aldehyde 9 with Aniline: Isolation of dimer 13

Under stirring and set-up for the removal of water formed in the reaction, a suspension of the aldehyde 9 (1.354 g, 7.2 m mol) was admixed with aniline(0.813 g, 8.7 m mol), the mixture refluxed for 4.0 hr, cooled, filtered, washed with dry benzene till the filtrate was colourless, dried *in vacuo* to give 0.475 g (15.2%) of 13, mp. 235°C. The filtrates did not yield any pure compound.

Mass:m/e: 433 (M^+), 287 (M^+ - ).

Anal. Calcd. for $C_{26}H_{19}N_5O_2$ (Mol. Wt. 433).

C, 72.05; H, 4.39; N, 16.17%

Found C, 72.41; H, 4.36; N, 16.2 %

ir : ν_{max}(KBr) cm^{-1}: 3310 (N-H), 1690 (amide carbonyl), 1630, 1600, 1566 (C=C, C=N).

nmr: δ(DMSO-d_6) 500 MHz: 6.25, 6.3 (d,d,1H, CH=C<u>H</u>-Q), 8.48, 8.66 (s,s,1H, NH-C<u>H</u>=CH), 6.75-8.25 (m, 15H, aromatic), 8.66 (m, 1H, CH=C-C<u>H</u>=CH-).

XVI. Reaction of <u>3</u> with Allyl bromide: Preparation of 6-Nitro-3-allyl-3,4-dihydro-4-oxoquinazoline (<u>14</u>)

To a stirred solution of 6-nitro-3,4-dihydro-4-oxo-quinazoline <u>3</u> (4.75 g, 24.9 m mol) in dry methanol (100 ml) was added KOH pellets (1.48 g, 26 m mol) followed by allyl bromide (3.1 g, 26 m mol). The reaction mixture was refluxed for 3 hr during which a clear solution was obtained and the product formation complete (tlc). Solvents were evaporated <u>in vacuo</u>, the residue extracted with dry benzene, transferred to a column of silicagel. Elution with Ph:EtOAc::1:1 gave 4.011 g, (69.8%) of <u>14</u>, mp. 148-150°C.

tlc: EtOAc. Rf. 0.6.

Anal. Calcd for $C_{11}H_9N_3O_3$ (Mol. Wt. 231).

C, 57.14; H, 3.89%

Found C, 57.17; H, 4.12%

ir : ν_{max}(KBr) cm^{-1}: 1675 (amide carbonyl), 1615, 1600, 1570 (C=C, C=N), 1520, 1360 (NO_2).

nmr: δ($CDCl_3$) 200 MHz: 4.54 (d, 2H, N-$\underline{CH}_2$), 5.2 (m, 2H, CH=$\underline{CH}_2$), 5.84 (m, 1H, $\underline{CH}$=CH_2), 7.66 (d, 1H, 8'-quinazoline ring) 8.08 (s, 1H, 2'-quinazoline ring), 8.35 (dd, 1H, 7'-quinazoline ring), 8.85 (d, 1H, 5'-quinazoline ring).

XVII. Reaction of 14 with 2,2-Diethoxy-1-bromoethane: Preparation of 6-Nitro-3-(2'-Diethoxyethyl)-3,4-dihydro-4-oxoquinazoline (15)

6-Nitro-3,4-dihydro-4-oxoquinazoline (5.0 g, 26 m mol) was introduced into a solution of sodium methoxide-prepared from sodium (0.625 g, 27 m mol) and methanol (75 ml) - and the solvents evaporated in vacuo from the resulting clear yellow solution. The residue was powdered, admixed with HMPA (30 ml), left stirred at 40-50°C for 1 hr and to the resulting clear solution was added 2',2'-diethoxy-1-bromo ethane (bromo acetaldehyde diethyl acetal) (5.69 g, 28.8 m mol) and the mixture left stirred at 90-100°C for 24 hr. The viscous brown solution was poured over crushed

ice (~ 1 kg), filtered and dried to give 5.83 g (69.7%) of 6-Nitro-3-(2'-diethoxyethyl)-3,4-dihydro-4-oxoquinazoline (15), as shiny plates, mp. 122-3°C.

tlc: EtOAc: Rf. 0.9

Anal. Calcd for $C_{14}H_{18}N_2O_3$ (Mol. Wt. 262).
C, 54.7; H, 5.53; N, 13.68%
Found C, 55.1; H, 5.26; N, 14.0 %

ir : ν_{max}(KBr) cm^{-1}: 1690 (amide carbonyl), 1615, 1600, 1570 (C=C, C=N), 1525, 1350 (NO_2).

nmr: δ($CDCl_3$) 200 MHz: 1.2 (t, 6H, -O-CH_2-CH_3), 3.6, 3.85 (m, m, 4H, -O-CH_2-CH_3), 4.15 (d, 2H, N-CH_2-), 4.8 (t, 1H, N-CH_2-CH-), 7.9 (d, 1H, 8'-quinazoline ring), 8.3 (s, 1H, 2'-quinazoline ring), 8.6 (dd, 1H, 7'-quinazoline ring), 9.2 (d, 1H, 5'-quinazoline ring).

XVIII. Hydrolysis of ketal 15: Isolation of Nitroaldehyde 16

A stirred suspension of the nitroacetal 15 (0.8 g, 3 m mol) in ice-cold conc. H_2SO_4 (3 ml) was gradually heated to 80-90°C. The resulting clear solution was cooled, poured over crushed ice (~ 150 g), filtered, washed with chilled water (3 x 100 ml) and air dried. The combined filtrates were admixed with aqueous ammonia to pH 6-7, filtered, washed with distilled water

(3 x 100 ml) to give a second lot of the aldehyde. Crystallisation from ethyl acetate gave 0.46 g (75.8%) of 16, mp. 180-3°C.

tlc: EtOAc: Ref. 0.7

Mass: m/e: 233 (M^+), 205 (M^+-CO).

Anal. Calcd for $C_{10}H_7N_3O_4$ (Mol. Wt. 233)
C, 51.5; H, 3.0; N, 18.02%
Found C, 51.8; H, 3.07; N, 18.46%

ir : ν_{max}(KBr) cm^{-1}: 1730 (aldehyde), 1690 (amide carbonyl) 1615, 1605 (C=C, C=N), 1525, 1345 (NO_2).

nmr: $\delta(CDCl_3)$ 200 MHz: 5.0 (s, 2H, $-CH_2-CHO$), 7.95 (d, 1H, 8'-quinazoline ring), 8.08 (s, 1H, 2'-quinazoline ring), 8.65 (d.d, 1H, 7'-quinazoline ring), 9.2 (d, 1H, 5'-quinazoline ring), 9.85 (s, 1H, -CHO).

XIX. Attempted Schiff base formation of aldehyde 16: Isolation of Nitro aminal 16a

Under stirring and set-up for removal of water formed during the reaction, ammonia was passed through a refluxing solution of the nitro aldehyde 16 (0.462 g, 2 m mol) for 3 hr. The pale yellow solid that separated was filtered, washed with dry benzene, and dried in vacuo to give 0.4g (80.7%) of the aminal 16a, mp. 220°C (dec).

Anal. Calcd for $C_{10}H_{10}N_4O_4$ (Mol. Wt. 250)

C, 48.0; H, 4.0 ; N, 22.4%

Found C, 48.6; H, 3.78 ; N, 22.7%

ir : ν_{max}(KBr) cm^{-1}: 3500 (br, OH), 3290 (NH), 1680 (amide carbonyl), 1610, 1570 (C=C, C=N), 1340, 1520 ($-NO_2$).

XX. Alkylation of 2 with 2-Bromoethanol: Preparation of 3-(2'-Hydroxyethyl)-3,4-dihydro-4-oxoquiazoline (17)

Under stirring 3,4-Dihydro-4-oxoquiazoline 2 (2.92 g, 20 m mol) was added to a solution of sodium methoxide-prepared from sodium (0.5 g, 21 m mol) and methanol (50 ml) - followed by bromoethanol (2.75 g, 21 m mol) and the mixture refluxed for 24 hr. Solvents were evaporated *in vacuo*, the residue was admixed with water (150 ml), saturated with NaCl, extracted with ethyl acetate (3 x 100 ml), washed with 5% NaOH solution (2x50 ml saturated brine (50 ml), dried ($MgSO_4$) and evaporated to give 2.35 g (62%) of 17, mp. 157°C (lit.[40] 155°C).

ir : ν_{max}(KBr) cm^{-1}: 3250 (OH), 1670 (amide carbonyl), 1610, 1560 (C=C, C=N).

nmr: δ(DMSO-d_6) 500 MHz: 3.7 (2H, -N-CH_2), 4.05 (2H, -CH_2-OH), 4.5-8.3 (5H, -aromatic).

XXI. Sodium borohydride reduction of the aldehyde 7: Correlation of structure with alcohol 17

Under ice-cooling and stirring $NaBH_4$ (0.315 g, 8.5 m mol) was added to a suspension of the aldehyde 7 (0.078 g, 4 m mol) in dry methanol (20 ml). The resulting clear solution was admixed with acetic acid (0.25 ml), solvents evaporated and the residue chromatographed on silica gel. Elution with EtOAc gave 0.675 g (85.6%) of 17, mp. 157°C whose properties were identical to that obtained from experiment XX.

XXII. PCC oxidation of alcohol 17: Correlation of structure with aldehyde 7

A solution of 17, (0.1 g, 0.53 m mol) in CH_2Cl_2 (50 ml) was added during 0.5 hr to an ice cold and stirred solution of pyridinium chlorochromate (0.16 g, 0.75 m mol) in dry methylene chloride (20 ml). The reaction mixture was left stirred at 0°C for 1 hr and then at rt for 3 hr. Tlc in ethyl acetate showed complete conversion of alcohol 17 to the aldehyde 7.

XXIII. Attempted cyclisation of the alcohol 17 with Potassium t-butoxide in t-butanol

Under nitrogen and stirring, the alcohol 17 (1.0 g, 5.2 m mol) was added to KOtBu in tBuOH - prepared from potassium

(0.41 g, 1.05 m mol) and t-BuOH (30 ml) - and the solution refluxed for 3 hr, solvents evaporated, the residue admixed with water, adjusted to pH 7 with conc. HCl, extracted with EtOAc, dried ($MgSO_4$) and evaporated to give 0.875 g of unchanged 17.

XXIV. Reaction of alcohol 17 with AC_2O: Preparation of acetate 18

A solution of 17 (1.0 g, 5.26 m mol) in pyridine:acetic anhydride (1:1, 2 ml) was warmed in a waterbath for 0.5 hr, solvents evaporated in vacuo, the residue admixed with benzene and evaporated to remove traces of pyridine and Ac_2O and the residue on crystallisation gave 1.15 g (98%) of 18, mp. 79°C.

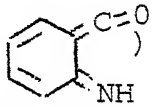
Anal. Calcd for $C_{12}H_{12}N_2O_3$ (Mol. Wt. 232).
C, 62.06; H, 5.17%
Found C, 62.06; H, 5.64%

nmr: $\delta(CDCl_3)$ 60 MHz: 2.1 (s, 3H, CO-CH_3), 4.4 (m, 4H, CH_2-CH_2-O), 7.5-7.9 (m, 3H, 6',7',8'-quinazoline ring), 8.1 (s, 1H, 2'-quinazoline ring), 8.4 (d, 1H, 5'-quinazoline ring).

XXV. Reaction of 3,4-Dihydro-4-oxoquinazoline with Nitroethylene: Preparation of 3-(2'-Nitroethyl)-3,4-dihydro-4-oxoquinazoline 19

To a stirred and ice-cold solution of 3,4-Dihydro-4-oxoquinazoline 2 (1.0g, 6.8 m mol) in dry ethylacetate (150 ml),

was added, over 0.75 hr, a 10% solution of nitroethylene in benzene (10 ml, 13.6 m mol) and the mixture left stirred at rt for 36 hr. Solvents were evaporated in vacuo and the residue chromatographed on silica gel. Elution with benzene:ethyl acetate ::9:1 gave nearly pure 19 which was crystallised from benzene: petroleum ether::2:1; yield 1.32 g (88%) mp. 118-9°C.

Mass:m/e: 219 (M^+), 173 (M^+-NO_2), 159 ($M^+-CH_2-NO_2$), 145 ($M^+-CH_2-CH_2-NO_2$), 119 ().

Anal. Calcd for $C_{10}H_9N_3O_3$ (Mol. Wt. 219).

C, 54.79; H, 4.11; N, 19.16%

Found C, 54.8 ; H, 4.32; N, 19.42%

ir : ν_{max}(KBr) cm^{-1}: 1660 (amide carbonyl), 1615 (C=C), 1550, 1355 (NO_2).

nmr: $\delta(CDCl_3)$ 500 MHz: 4.54 (t, 2H, N-CH_2), 4.88 (t, 2H, CH_2-NO_2), 7.53, 7.78 (t,t, 1H, 1H, 6',7'-quinazoline ring), 7.72 (d, 1H, 8'-quinazoline ring), 8.1 (s, 1H, 2'-quinazoline ring), 8.28 (d, 1H, 5'-quinazoline ring).

XXVI. Attempted "Nef" reaction of the nitroethyl oxoquinazoline 19:

a) Preparation of the nitronate salt 20

Under ice-salt cooling and stirring, a solution of the nitroethyl quinazoline (0.438 g, 2 m mol) in methanol (2 ml) was

admixed with sodium methoxide - prepared from sodium (0.092 g, 4 m mol) and methanol (10 ml) - the mixture left stirred for 0.5 hr, dry ether introduced, filtered, washed with dry ether and dried in vacuo and the dry nitronate salt 20 was used as such in the subsequent reaction.

ir : ν_{max}(KBr) cm^{-1}: 3500 br (salt), (1530-NO_2 absent).

b) Reaction of nitronate 20 with acid: Isolation of 19

The above salt was added in small portions to ice cold conc. H_2SO_4 (5 ml), the solution gradually warmed to 50°C, cooled, poured over crushed ice (~ 50 g), neutralised with NH_4OH, extracted with ethyl acetate, and solvents evaporated to yield 0.39 g (90%) unchanged 3-(2'-Nitroethyl)-3,4-dihydro-4-oxoquinazoline 19.

XXVII. Reduction of 3(2'-Nitroethyl)-3,4-dihydro-4-oxoquinazoline 19 with Sn and HCl: Preparation of amine dihydrochloride 21

To conc. HCl (5 ml) maintained at 50-60°C was added the nitroethyl oxoquinazoline (0.5 g, 2.3 m mol), in portions followed by firely shredded tin metal (0.5 g, 4.2 m mol) and heating continued for 0.5 hr. The resulting clear yellow solution was evaporated to dryness, the residue dissolved in water (~ 10 ml), the Sn precipitated as SnS by passage of H_2S for 0.25 hr, filtered, evaporated, triturated with ethyl acetate, the residue dried in vacuo, dissolved in minimum amount of absolute methanol,

precipitated with dry ether, filtered, re-dissolved in methanol, re-precipitated with dry ether and filtered to give 0.310 g (60.2%) of the amine dihydrochloride 21, mp. 259-60°C (dec) (lit.[39] 260°C (dec)).

ir : ν_{max}(KBr) cm^{-1}: 3400-3200 br (NH salt), 1710 (amide carbonyl).

XXVIII. Reaction of base 21 with benzoyl chloride: Preparation of the benzamide 22

A solution of the dihydrochloride of 3 -(2'-amino ethyl)-3,4-dihydro-4-oxoquinazoline 21 (0.3g, 1.15 m mol) in water (5 ml) was admixed with benzoylchloride (0.4 ml, 3.45 m mol) and 2N NaOH (4 ml, 8.0 m mol). The mixture was shaken for 0.25 hr, filtered, washed with water, dried and recrystallised from ethylacetate: hexane::1:2 to give 0.237 g (70%) of the 3-(2'-N-Benzoylamino)-3,4-dihydro-4-oxoquinazoline 22, mp. 176-77°C.

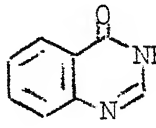
Anal. Calcd for $C_{17}H_{15}N_3O_2$ (Mol. Wt. 293)
C, 69.62; H, 5.12; N, 14.33%
Found C, 69.81; H, 5.04; N, 14.64%

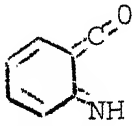
ir : ν_{max}(KBr) cm^{-1}: 3300 (NH), 1670 (amide carbonyl), 1625, 1530 (secondary amide).

nmr: $\delta(CDCl_3)$ 200 MHz: 3.74 (q, 2H, $C\underline{H}_2$-NH), 4.22 (t, 2H, N-$C\underline{H}_2$), 7.25-7.8 (m, 9H, aromatic, N$\underline{H}$), 7.9 (s, 1H, 2'-quinazoline ring), 8.1 (d, 1H, 5'-quinazoline ring).

XXIX. Reaction of 3,4-dihydro-4-oxoquinazoline 2 with Acrolein: Isolation of the tricyclic oxazino quinazolone 23 and 3-(3'-oxo-n-propyl)-3,4-dihydro-4-oxoquinazoline 24

Under stirring and protection from moisture, at rt. a suspension of 3,4-dihydro-4-oxoquinazoline 2, (1.0 g, 6.9 m mol) in dry methanol (20 ml) was admixed with acrolein (2 ml, 30 m mol) followed by triethylamine (2.5 ml, 18 m mol). The mixture was left stirred overnight, solvents evaporated, the viscous residue chromatographed on silica gel. Elution with benzene: ethylacetate::3:7 gave 1.362 g (98.4%) of mixture of the tricyclic system 23 and its aldehyde counterpart 24, mp. 79-81°C.

Mass:m/e: 202 (M^+), 174 (M^+-CO), 146 ()$^+$,

119 ()$^+$.

Anal. Calcd for $C_{11}H_{10}N_2O_2$ (Mol. Wt. 202).

C, 65.35; H, 4.95; N, 13.86%

Found C, 66.42; H, 5.10; N, 13.72%

ir : ν_{max}(KBr) cm^{-1}: 3120 (N-H), 1670 (amide carbonyl), 1620, 1560 (C=C, C=N).

nmr: $\delta(CDCl_3)$ 60 MHz: 3.1 (q, CH_2-C<u>H</u>=CH-O), 3.3 (d, ~70% C<u>H</u>$_2$-CH=CH-O), 4.1 (q, ~70% CH_2-CH=C<u>H</u>-O, 2'-quinazoline ring), 4.6 (br, ~70% N<u>H</u>), 9.7 (s, ~30% -C<u>H</u>O), 7.5-8.2 (m, 5H, aromatic).

XXX. Reaction of <u>2</u> with acrylonitrile: Preparation of 3-(2'-cyanoethyl)-3,4-dihydro-4-oxoquinazoline <u>26</u>

Under stirring and protection from moisture, a solution of <u>2</u> (5.0g, 34.2 m mol) in dry methanol (100 ml) was admixed with triethyl amine (5 ml, 36 m mol) followed by acrylonitrile (5 ml, 76 m mol), left stired at rt for 12 hr, filtered, washed with chilled dry methanol (3x25 ml), dried <u>in vacuo</u> and crystallised from benzene:hexane::2:1 to give 6.264g (91.9%) of <u>26</u>, mp. 144-5°C (lit.[44] mp. 136-8°C).

Anal. Calcd for $C_{11}H_9N_3O$ (Mol. Wt. 199).
C, 66.3: H, 4.52; N, 21.1%
Found C, 66.3; H, 4.85; N, 21.61%

ir: ν_{max}(KBr) cm^{-1}: 2250 (C≡N), 1670 (amide carbonyl), 1610 (C=C).

nmr: $\delta(CDCl_3)$ 60 MHz: 2.85 (t, 2H, -C<u>H</u>$_2$-CN), 4.2 (t, 2H, -C<u>H</u>$_2$-CH_2-CN), 7.5 (m, 3H, 6',7',8'-quinazoline ring), 8.1 (s, 1H, 2'-quinazoline ring), 8.25 (m, 1H, 5'-quinazoline ring).

XXXI. Reaction of 2 with 1,2-Dibromo ethane: Preparation of 3-(2'-Bromoethyl)-3,4-dihydro-4-oxoquinazoline 27

Under stirring and protection from moisture, 3,4-dihydro-4-oxoquinazoline 2 (5 g, 34.2 m mol) was added to a solution of sodium methoxide - prepared from sodium (0.8 g, 34.7 m mol) and dry methanol (50 ml) - left stirred at rt for 1 hr, solvents evaporated, the residue suspended in dry HMPA (25 ml), admixed with 1,2-Dibromoethane (7.63 g, 40.6 m mol), left stirred at rt for 12 hr, and then at 60°C for another 12 hr. The reaction mixture cooled, poured over ice-water (1 lit), filtered, washed with ice-water (4 x 50 ml), dried, and crystallised from benzene: hexane ::1:1 to give 4.66 g (54%) of 27, mp. 116°C (lit.[43] mp.114°C).

Tlc:ethyl acetate: Rf. 0.65.

ir : ν_{max}(KBr) cm^{-1}: 1670 (amide carbonyl), 1620, 1610, 1560 (C=C, C=N).

nmr: $\delta(CDCl_3)$ 60 MHz: 3.7 (t, 2H, N-CH_2), 4.35 (t, 2H, -CH_2-Br), 7.2-7.8 (m, 3H, 6',7',8'-quinazoline ring), 8.05 (s, 1H, 2'-quinazoline ring), 8.2 (m, 1H, 5'-quinazoline ring).

XXXII. Reaction of 3-(2'-bromoethyl)-3,4-dehydro-4-oxoquinazoline 27 with aniline: Preparation of 3-(2'-anilinoethyl)-3,4-dihydro-4-oxoquinazoline (28)

Under stirring, a solution of 27 (0.253 g, 1 m mol) in absolute ethanol (25 ml) was admixed with a solution of aniline (0.186 g, 2 m mol), refluxed for 8 hr, solvents evaporated *in vacuo*, the residue admixed with water (15 ml), extracted with benzene (3 x 25 ml), dried ($MgSO_4$), evaporated, and the residue chromatographed on silicagel. Elution with benzene:ethyl acetate::7:3 gave 0.25 g (94.3%) of 28, mp. 143-5°C

Tlc:benzene:ethyl acetate::1:1: Rf . 0.45

Ancl. Calcd for $C_{16}H_{15}N_3O$ (Mol. Wt. 265).

C, 72.45; H, 5.66%

Found C, 72.85; H, 5.61%

ir : ν_{max}(KBr) cm^{-1}: 3260 (NH), 1675 (amide carbonyl), 1600, 1560 (C=C, C=N).

nmr: $\delta(CDCl_3)$ 60 MHz: 3.5 (m, 2H, $-CH_2-NH-Ph$), 4.2 (m, 3H, $N-CH_2-CH_2-NH$), 6.4-6.78 (m, 8H, 6',7',8'-quinazoline ring,phenyl), 7.85 (s, 1H, 2'-quinazoline ring), 8.25 (m, 1H, 5'-quinazoline ring).

XXXIII. Reaction of 2 with hydrazine hydrate: Preparation of 3-Amino-3,4-dihydro-4-oxoquinazoline[45](29)

A mixture of 3,4-Dihydro-4-oxoquinazoline 2 (5 g, 34.2 m mol) and hydrazinehydrate (10 ml, excess) was refluxed for 0.25 hr, cooled, filtered, washed with chilled ethanol (3x10 ml) dried in vacuo and crystallised from hot ethanol to give 3.975 g (72.1%) of 29, mp. 208°C (lit.[45] mp. 204-8°C).

XXXIV. Formylation of 29: Preparation of 3-Formamido-3,4-dihydro-4-oxoquinazoline(30)

a) Preparation of acetic formic anhydride[48]

Under stirring freshly distilled acetic anhydride (1.2 ml, 2 eq) at ice-salt temp. was added, in drops to formic acid (98-100%) (0.6 ml, 1 eq), held at 50°C. The reaction mixture was left stirred for 0.25 hr and cooled to 0°C, prior to use in the following experiment.

b) Formylation of 29

Under protection from moisture, a mixture of 3-amino-3,4-dihydro-4-oxoquinazoline 29 (1 g, 6.2 m mol), pyridine (1.2 g, 15 m mol) and acetic formic anhydride (1.25 g, 15 m mol) was left stirred for 6 hr, poured over crushed ice, left aside for 0.25 hr filtered, washed with ethyl acetate, dried ($MgSO_4$),

evaporated, and crystallised from benzene:hexane::1:1 to give 0.96g (81.7%) of 3-formylamino-3,4-dihydro-4-oxoquinazoline 30, mp. 152-3°C.

ir : ν_{max}(KBr) cm^{-1}: 3420, 3181 (NH), 1710 (shoulder) (formyl), 1675 (ring amide), 1610, 1560 (C=C, C=N).

XXXV. Benzoylation of 3-Amino-3,4-dihydro-4-oxoquinazoline (29): Preparation of 3-Benzamido-3,4-dihydro-4-oxoquinazoline (31)

Under stirring, benzoyl chloride (6.3 g, 45 m mol) in dry benzene (50 ml) was added in 1 hr, to a suspension of 29 (4.84 g, 30 m mol) and pyridine (3.6 g, 45 m mol) in dry benzene (100 ml), left stirred at rt for 16 hr, admixed with distilled water (100 ml), left stirred for 2 hr, the aqueous layer extracted with ethyl acetate, the combined organic extracts washed with 2N NaOH (3 x 75 ml), the aqueous layer made acidic (pH3) with conc. HCl, filtered washed with water crystallised from hot ethyl acetate to give 7.1 g (89%) of 31, mp. 190-1°C (lit.[49] mp. 194°C).

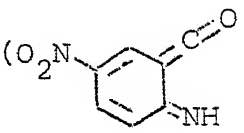
ir : ν_{max}(KBr) cm^{-1}: 3260 (N-H), 1660 (amide carbonyl), 1610, 1510 (C=C, C=N).

XXXVI. Reaction of 6-Nitro-3,4-dihydro-4-oxoquinazoline 3 with 80% Hydrazinehydrate: Isolation of 3-Amino-6-nitro-3,4-dihydro-4-oxoquinazoline (32) and 3-Amino-6-Nitro-3,4-dihydro-4-hydrazido quinazoline (33)

A mixture of 3 (5.0 g, 28.6 m mol) and 80% hydrazine-hydrate (10.5 ml, excess) was refluxed till evolution of ammonia ceased (0.25 hr), cooled, filtered, washed with chilled dry ethanol, dried in vacuo and the residue chromatographed on silicagel. Elution with ethylacetate gave 1.562 g (29%) of 32, mp. 220-22°C as an yellow powder.

Further elution with ethylacetate gave 0.335 g (5.8%) of 33, mp. 270°C (dec).

32: Tlc:ethylacetate:Rf. 0.75

Mass:m/e: 191 (M^+-NH), 165 ()$^+$, 119

Anal. Calcd for $C_8H_8N_4O_4$ (monohydrate) (Mol. Wt. 224).
C, 42.85; H, 3.57%

Found C, 43.8 ; H, 4.33%

ir : ν_{max}(KBr) cm^{-1}: 3500, 3380 (NH_2), 1660 (amide carbonyl), 1635, 1610, 1590 (C=C, C=N), 1300, 1490 (NO_2).

nmr: δ(DMSO-d_6) 100 MHz: 4.6 (br, 2H, $N\underline{H}_2$), 6.6 (d, 1H, 8'-quinazoline ring), 7.6 (s, 1H, 2'-quinazoline ring), 8.0 (dd, 1H, 7'-quinazoline ring), 8.4 (d, 1H, 5'-quinazoline ring).

33: tlc: ethyl acetate: Rf. 0.65.

ir : ν_{max}(KBr) cm^{-1}: 3460, 3420, 3340, 3300 (NH_2), 1670 (C=N-N), 1350, 1530 (NO_2).

nmr: δ(DMSO-d_6) 100 MHz: 5.7 (s, 2H, =N-$N\underline{H}_2$), 5.9 (s, 2H, -N-$N\underline{H}_2$), 7.2 (d, 1H, 8'-quinazoline ring), 7.4 (s, 1H, 2'-quinazoline ring), 7.6 (d, 1H, 7'-quinazoline ring), 8.1 (s, 1H, 5'-quinazoline ring).

XXXVII. Reaction of Hypoxanthine(34) with $POCl_3$: Preparation of 6-Chloropurine[53] (35)

A stirred mixture of hypoxanthine (10 g, 71.3 m mol), $POCl_3$ (60 ml), N,N-Dimethylaniline (30 ml) and toluene (100 ml), was refluxed for 2 hr, cooled, poured over crushed ice (400 g), adjusted to pH 10-11 with 10N NaOH, the blue toluene layer discarded, shaken with toluene (15 ml), the organic layer discarded, the aqueous layer kept overnight in the fridge, the sodium phosphate separated filtered, the filtrate cooled in ice, adjusted to pH 2, with conc. HCl, extracted with ether (8 x 250 ml), then with ethyl acetate (3 x 250 ml), the organic extracts

dried ($MgSO_4$) and evaporated to give 6.7g (58.9%) of 6-chloropurine 35, mp.>360°C (lit.[53] mp.>360°C).

XXXVIII. Benzylation of 6-chloropurine (35) with Benzylchloride in DMSO and K_2CO_3: Preparation of 7-Benzyl-6-chloropurine 36 and 9-Benzyl-6-chloropurine (37)

Under stirring and protection from moisture, freshly distilled benzyl chloride (10.2g, 80.6 m mol) followed by freshly ignited K_2CO_3 (6g, 43.4 m mol) was added to a solution of 35 (6.0g, 38.8 m mol) in dry DMSO (100 ml), left stirred at rt for 24 hr during which the alkylation was complete. The mixture was filtered, washed with DMSO (10 ml) admixed with water (150 ml), the precipitated viscous oil separated, the aqueous layer extracted with ether (3x25 ml), dried ($MgSO_4$), evaporated, the two lots combined, triturated with dry ether, and filtered to give 1.98g (21%) of 7-Benzyl-6-chloropurine 37 as a white crystalline solid, mp. 152°C (lit.[54] mp. 152-3°C).

The ether filtrate was evaporated, the residue extracted with hot petroleum ether (500 ml), evaporated and the residue on crystallisation from petroleum ether gave 4.27g (45%) of 9-Benzyl-6-chloropurine 36, mp. 89°C (lit.[54] mp. 87-9°C).

36: tlc:benzene:dioxane:acetic acid::80:40:1; Rf. 0.75

ir : ν_{max}(KBr) cm^{-1}: 3100, 3050 (aromatic CH), 1600, 1560, 1540 (C=C, C=N).

nmr: $\delta(CDCl_3)$ 60 MHz: 5.45 (s, 2H, $-C\underline{H}_2-\emptyset$), 7.3 (s, 5H, phenyl), 8.1 (s, 1H, imidazole ring), 8.7 (s, 1H, pyrimidine ring).

37: Tlc:benzene:dioxane:acetic acid::80:40:1; Rf. 0.65.

ir : ν_{max}(KBr) cm^{-1}: 3100, 3075 (aromatic CH), 1600, 1540, 1525 (C=C, C=N).

nmr: $\delta(CDCl_3)$ 60 MHz: 5.7 (s, 2H, $C\underline{H}_2-\emptyset$), 7.3 (m, 5H, phenyl), 8.3 (s, 1H, imidazole ring), 8.8 (s, 1H, pyrimidine ring).

XXXIX. Alkylation of 9-Benzyl-6-Chloropurine(36): Preparation of 6-Allyloxy-9-benzyl-purine(38)

Under stirring and protection from moisture, 9-Benzyl-6-chloropurine (1.5 g, 61 m mol) was added to a solution of sodium allyloxide in allyl alcohol - prepared from sodium (0.14 g, 61 m mol) and dry allyl alcohol (20 ml) - refluxed for 1.5 hr, filtered, solvents evaporated *in vacuo*, the residue triturated with hot benzene (50 ml), cooled, decanted and evaporated to give 1.15 g (70.4%) of 6-allyloxy-9-benzylpurine as colourless crystals mp. 65°C.

Anal. Calcd for $C_{15}H_{14}N_4O$ (Mol. Wt. 266)
C, 67.67; H, 5.26%
Found C, 67.87; H, 5.43%

ir : ν_{max}(KBr) cm^{-1}: 3080, 3020 (aromatic, olefinic C-H), 1600, 1580 (C=C, C=N), 1050 (C-O).

nmr: $\delta(CDCl_3)$ 60 MHz: 5.1 (m, 2H, -O-$C\underline{H}_2$), 5.38 (m, 4H, -$C\underline{H}_2$-Ø, CH=$C\underline{H}_2$), 6.18 (m, 1H, -$C\underline{H}$=CH_2), 7.28 (s, 5H, phenyl), 7.8 (s, 1H, imidazole ring), 8.5 (s, 1H, pyrimidine ring).

XL. Claisen Rearrangement of the allyl ether 38: Isolation of 1-Allyl-9-benzyl-6-oxopurine(40)

1-Allyloxy-9-benzyl purine 38 (1.0g, 3.76 m mol) was sealed under nitrogen, held at 180-90°C for 6 hr, extraction with CH_2Cl_2, the organic extract passed through a colum of silica, and then through a bed of activated charcoal, evaporated and crystallised from benzene:hexane::1:1 to give (0.291 g, 29%) of 1-allyl-9-benzyl-6-oxopurine as a white crystalline solid, mp. 114-5°C.

Anal. Calcd for $C_{15}H_{14}N_4O$ (Mol. Wt. 266)
C, 67.67; H, 5.26%
Found C, 67.84; H, 4.88%

ir : ν_{max}(KBr) cm^{-1}: 3100, 3040 (aromatic and olefinic C-H), 1685 (amide carbonyl), 1580, 1545, 1515 (C=C, C=N).

nmr: $\delta(CDCl_3)$ 60 MHz: 4.6 (dd, 2H, N-$C\underline{H}_2$), 5.2 (m, 4H, -$C\underline{H}_2$-Ø, -CH=$C\underline{H}_2$), 5.9 (m, 1H, -$C\underline{H}$=CH_2), 7.2 (s, 5H, phenyl), 7.6 (s, 1H, imidazole ring), 7.9 (s, 1H, pyrimidine ring).

XLI. Alkylation of 7-Benzyl-6-chloropurine (37): Preparation of 6-Allyloxy-7-benzylpurine (39)

Under stirring and protetion from moisture, 7-Benzyl-6-chloropurine (2.0 g, 8.2 m mol) was added to a solution of sodium allyl oxide in dry allyl alcohol - prepared from sodium (0.21 g, 9.1 m mol) and allyl alcohol (20 ml, excess), refluxed for 1.5 hr, filtered, solvents evaporated *in vacuo*, the residue extracted with hot benzene, evaporated and crystallised from benzene:ethyl acetate::1:1, to give 1.632 g (75%) of 6-Allyloxy-7-benzylpurine 39, mp. 84°C.

Anal. Calcd for $C_{15}H_{14}N_4O$ (Mol. Wt. 266)
C, 67.67; H, 5.26%
Found C, 67.77; H, 5.43%

ir : ν_{max}(KBr) cm^{-1}: 3110, 3060 (aromatic and olefinic C-H), 1620, 1590, 1550 (C=C, C=N), 1070 (C-O).

nmr: $\delta(CDCl_3)$ 60 MHz: 5.0 (dd, 2H, O-$C\underline{H}_2$), 5.3 (m, 2H, -CH=$C\underline{H}_2$), 5.5 (s, 2H, $C\underline{H}_2$-Ph), 5.9 (m, 1H, $C\underline{H}$=CH_2), 7.1 (s, 5H, phenyl), 8.0 (s, 1H, imidazole ring), 8.5 (s, 1H, purine ring).

XLII. Regioselective alkylation of 6-chloropurine 35 with Dihydropyran: Preparation of 9-(2'-Tetrahydropyranyl)-6-chloropurine[55] (41)

Under stirring and protection from moisture a solution of 2,3-dihydropyran (1 ml, 10.9 m mol) in ethyl acetate (30 ml) was added over 0.5 hr to a solution of 6-chloropurine 35 (1.0 g, 6.51 m mol) in dry ethyl acetate (30 ml) held at 60°C and admixed with PTSA (0.02 g, 0.105 m mol). The reaction mixture was left stired for additional 1 hr at rt, admixed with NH_4OH (0.5 ml, sp. gr. 0.89) left stirred for 0.1 hr, washed with water, dried ($MgSO_4$), solvents evaporated in vacuo, the residue crystallised from hexane to give 1.235 g (80%) of 41, mp. 69°C (lit.[55] mp. 69-71°C).

ir : ν_{max}(KBr) cm^{-1}: 3110 (aromatic C-H), 2940, 2880 (saturated C-H), 1595, 1565 (C=C, C=N).

XLIII. Alkylation of 41: Preparation of 9-(2'-Tetrahydropyranyl)-6-allyloxypurine (42)

Under stirring and protection from moisture 9-(2'-Tetrahydropyranyl)-6-chloropurine 41 (2 g, 8.3 m mol) was added to a solution of sodium allyloxide - prepared from sodium (0.212 g, 9.2 m mol) and dry allyl alcohol (20 ml) - refluxed for 3 hr, solvents evaporated in vacuo, the residue triturated with hot

dry benzene, decanted, evaporated, the thick viscous residue distilled to give 1.8 g (82.55%) of 9-(2'-Tetrahydropyranyl)-6-allyloxy purine 42, bp. 180-90°C/0.15 mm.

Anal. Calcd for $C_{13}H_{16}N_4O_2$ (Mol. Wt. 260)
C, 60.0; H, 6.15; N, 21.54%
Found C, 59.6; H, 5.73; N, 22.34%

ir : ν_{max}(neat) cm^{-1}: 3060 (aromatic and olefinic C-H), 2940, 2850 (sat. C-H), 1590, 1570, 1555 (C=C, C=N), 1040, 1050 (C-O).

nmr: $\delta(CDCl_3)$ 60 MHz: 1.9 (m, 6H, THP), 3.9 (m, 2H, -O-CH_2-THP ring), 5.0 (dd, 2H, O-CH_2-CH-THP ring), 5.1-6.35 (m, 4H, $CH=CH_2$, O-CH- THP ring), 7.9 (s, 1H, imidazole ring), 8.5 (s, 1H, pyrimidine ring).

XLIV. Reaction of 9-Benzyl-6-chloropurine(36) with HCl: Preparation of 9-Benzyl hypoxanthine(43)

1N-HCl (8 ml) was added to a suspension of 9-Benzyl-6-chloropurine(36), in water (25 ml), the mixture refluxed for 0.2 hr, cooled, filtered, washed with water (3 x 5 ml), crystallised from hot water, and dried at 90-100°C to give 0.7 g (75.7%) of 43, mp. 293°C (lit.[57] mp. 295-7°C).

ir : ν_{max}(KBr) cm^{-1}: 1700 (amide carbonyl), 1590, 1550, 1520 (C=C, C=N).

XLV. Alkylation of 9-Benzyl hypoxanthine (43) with 2-Bromo-1,1-diethoxy ethane: Preparation of 1-(2'-diethoxy ethyl)-9-benzyl-6-oxopurine (44)

9-Benzyl hypoxanthine 43 (1 g, 4.42 m mol) was added to a solution of sodium methoxide in methanol - prepared from sodium (0.112 g, 4.87 m mol) and dry methanol (20 ml) - left stirred for 1 hr, solvents removed from the resulting clear solution in vacuo, the residue suspended in HMPA (12 ml), held at 60°C, and under stirring, admixed with 2-Bromo-1,1-diethoxy ethane (0.955 g, 4.84 m mol). The reaction mixture was left stirred for 24 hr, poured over water (400 ml), extracted with ethyl acetate (3 x 150 ml), washed with brine (2 x 50 ml), dried ($MgSO_4$) and evaporated to give 0.72 g (47.5%) 1-(2'-Diethoxy-ethyl)-9-benzyl hypoxanthine (44), mp. 119-20°C.

tlc: ethyl acetate: Rf. 0.6

Anal. Calcd for $C_{18}H_{22}N_4O_3$ (Mol. Wt. 342)
C, 63.12; H, 6.43; N, 16.34%
Found C, 63.46; H, 6.13; N, 16.3 %

ir : ν_{max} (KBr) cm^{-1}: 1685 (amide carbonyl), 1570, 1540, 1505 (C=C, C=N).

nmr: $\delta(CDCl_3)$ 200 MHz: 1.08 (t, 6H, $-O-CH_2-\underline{CH_3}$), 3.46, 3.70 (m, m, 2H, 2H, $-O-\underline{CH_2}-CH_3$), 4.1 (d, 2H, $N-\underline{CH_2}-CH$), 4.68 (t, 1H, $N-CH_2-\underline{CH}$), 5.28 (s, 2H, $N-\underline{CH_2}-\emptyset$), 7.26 (m, 5H, phenyl), 7.7 (s, 1H, imidazole ring), 7.98 (s, 1H, pyrimidine).

XLVI. Acid Hydrolysis of acetal(44):Preparation of 1-(2'-Oxo-ethyl)-9-benzyl hypoxanthine(45)

A suspension of the acetal (44) (0.44g, 1.27 m mol) in conc. H_2SO_4) (2.5 ml) was held at 80-90°C for 0.05 hr, cooled and poured over crushed ice (150 g) adjusted to pH 6-7 with liquor ammonia, filtered, the aqueous layer saturated with NaCl, extracted with ethyl acetate (3 x 75 ml), dried ($MgSO_4$) and solvents evaporated to give a second lot of the aldehyde. The combined productson crystallisation from hot ethyl acetate gave 0.211 g (61.9%) of aldehyde 45, mp. 130°C.

Mass:m/e: 269 $(M + 1)^+$, 268 (M^+), 240 (M^+-CO), 149 $(M^+-CO-CH_2-\emptyset)$, 91 $(.CH_2-C_6H_5)^+$.

Anal. Calcd for $C_{14}H_{12}N_4O_2$ (Mol. Wt. 268).
C, 62.68; H, 4.47; N, 20.89%
Found C, 62.37; H, 4.58; N, 20.72%

ir : ν_{max}(KBr) cm^{-1}: 1670 (br),(aldehyde and amide carbonyl), 1570, 1550, 1515 (C=C, C=N).

XLVII. Attempted Schiff base formation of 45 with ammonia: Isolation of aminal 46

Under stirring and set-up for the removal of water formed in the reaction, dry NH_3 was passed through a refluxing suspension of the aldehyde 45, (0.15 g, 0.564 m mol) in dry benzene for 2 hr, cooled filtered, washed with dry benzene to give 0.114 g (71.4%) of the aminal 46, mp. 170°C (dec).

Anal. Calcd for $C_{14}H_{15}N_5O_2$ (Mol. Wt. 285).
C, 58.96; H, 5.26; N, 24.5%
Found C, 59.12; H, 5.53; N, 24.3%

ir : ν_{max}(KBr) cm^{-1}: 3500-3300 (br),(OH), 3300, 3100 (NH), 1675 (amide carbonyl).

XLVIII. Reaction of 3-Allyl-3,4-dihydro-4-oxoquinazoline(6) with acetyl chloride: Isolation of O-Acetyl salt 47

Under stirring and protection from moisture, a mixture of 3-Allyl-3,4-dihydro-4-oxoquinazoline 6 (1 g, 6.85 m mol) and acethyl chloride (15 ml, excess) was left stirred for 2 hr, evaporated *in vacuo*, admixed with dry ether and evaporated *in vacuo* to give 1.398 g, 98.3% of the acetyl salt 47, mp. (sinters at 120°C and melts at 145-50°C).

Anal. Calcd for $C_{13}H_{13}N_2O_2Cl$ (Mol. Wt. 264.5).

C, 58.97; H, 4.91; N, 10.58%

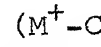
Found C, 58.91; H, 4.88; N, 10.75%

ir : ν_{max}(KBr) cm^{-1}: 2640 (br) (salt), 1715 (ester).

XLIX. Reaction of the O-Acetyl -salt 47 with methyllithium: Isolation of 2-Isopropylamino-N-allyl benzamide 48

Under nitrogen, ice-cooling and stirring, the O-Acetyl-salt 47 (1.28 g, 4.85 m mol), was added to a solution of methyllithium (0.22 g, 10 m mol) in dry ether (20 ml) - prepared from lithium (0.13 g) and methyliodide (1.38 g, 0.6 ml) - the reaction mixture left stirred for 8 hr, poured over saturated NH_4Cl, extracted with ethyl acetate, dried ($MgSO_4$), solvents evaporated, and the residue chromatographed on silicagel. Elution with benzene: ethyl acetate::9:1 gave 0.225 g (42.1%) of 48, (based on recovered starting material as 6 on further elution with benzene:ethyl acetate::4:1), bp. 110°C/0.3 mm.

48: tlc: benzene:ethyl acetate:Rf. 0.9.

Mass:m/e: 218 (M^+), 203 (M^+-CH_3), 160 (M^+-CH_3-HN ), 146 ($M^+-CH_3-H_2N$).

Anal. Calcd for $C_{13}H_{18}N_2O$ (Mol. Wt. 218).
C, 71.56; H, 8.26%
Found C, 71.3 : H, 8.2 %

ir : ν_{max}(neat) cm^{-1}: 3340 (N-H), 3090 (aromatic and olefinic C-H), 2940, 2880 (saturated C-H), 1630 (amide carbonyl), 1580, 1520 (secondary amide).

nmr: δ($CDCl_3$) 200 MHz: 1.1 (d, 6H, -NH-CH-($C\underline{H}_3$)$_2$, 3.5 (sept. 1H, -$C\underline{H}$-(CH_3)$_2$, 3.86 (m, 2H, -NH-$C\underline{H}_2$-), 5.1 (m, 2H, -CH=$C\underline{H}_2$), 5.8 (m, 1H, -$C\underline{H}$=CH_2), 6.22 (br, 1H, -$N\underline{H}$-CH_2), 6.42 (t, 1H, 5'-anthranilic acid), 6.62 (t, 1H, 3'-anthranilic acid), 7.15 (m, 1H, 4'-anthranilic acid), 7.25 (d, 1H, 6'-anthranilic acid).

L. Attempted reaction of 3-Allyl-3,4-dihydro-4-oxoquinazoline(6) with methyllithium:

Under nitrogen stirring and ice-cooling 6 (0.5 g, 2.7 m mol) was added to a solution of methyllithium (0.141 g, 6.4 m mol) in ether (10 ml) - prepared from lithium (0.045 g) and methyliodide (0.445 g, 0.2 ml) - the reaction mixture left stirred for 8 hr, poured over saturated NH_4Cl , extracted with ethyl acetate, dried ($MgSO_4$), and evaporated to give 0.435 g (87%) of unchanged 6, mp. 65°C.

LI. Reaction of the O-Acetyl salt 47 with Sodiumhydride in 1,2-Dimethoxyethane: Isolation of 2-Formylamino-N-allyl benzamide (49)

Under stirring and nitrogen sodium hydride (1.04 g, 50% active, 22 m mol) was added to a suspension of the acetyl salt 47 (1.398 g, 5.3 m mol) in dry 1,2-Dimethoxyethane (100 ml), the mixture refluxed for 12 hr, cooled, poured over saturated NH_4Cl extracted with hexane to remove non polar residues then extracted with ethyl acetate, dried ($MgSO_4$) and the residue chromatographed on silicagel. Elution with benzene:ethyl acetate::9:1 gave 0.404 g, (69.3%) of 2-Formylamino-N-propenyl benzamide 49, mp. 109-11°C based on recovered starting material as 6 on further elution with benzene:ethyl acetate::17:3.

49: Mass:m/e: 204(M^+), 186 (M^+-H_2O), 148 (M^+-HN ), 120 (M^+-HN  - CO), 92 (M^+-HN-2CO).

Anal. Calcd for $C_{11}H_{12}N_2O_2$ (Mol. Wt. 204).
C, 70.21; H, 6.38; N, 14.89%
Found C, 70.23; H, 6.52; N, 15.0 %

ir : ν_{max}(KBr) cm^{-1}: 3300 (N-H), 1670 (amide carbonyl), 1640, 1600 (C=C), 1580, 1525 (secondary amide).

nmr: $\delta(CDCl_3)$ 200 MHz: 1.63 (dd, 3H, -CH-$C\underline{H}_3$), 4.9 (q, 1H, =$C\underline{H}$-CH_3), 6.7 (m, 1H, -N-$C\underline{H}$=CH), 6.98 (t, 1H, 5'-anthranilic acid), 7.35 (m, 2H, 3',4'-anthranilic acid), 7.95 (d, br, 1H, -CO-N$\underline{H}$-CH), 8.25 (d, 1H, NH-$C\underline{H}$O), 8.38 (d, 1H, 6'-anthranilic acid).

LII. Reaction of O-acetyl salt 47 with Methylmagnesium iodide: Isolation of 3- (1'-Propenyl)-3,4-dihydro-4-oxoquinazoline(50)

Under nitrogen stirring and ice-cooling, the acetyl salt 47 (1.58 g, 6 m mol) was added to a solution of methylmagnesium iodide (2.05 g, 12.5 m mol) in ether (20 ml) - prepared from magnesium (0.3 g) and methyl iodide (1.8 g) - the reaction mixture left stirred for 6 hr, poured on to saturated NH_4Cl, extracted with ethyl acetate, dried ($MgSO_4$) and solvents evaporated to give 1.065 g (95.85%) of 50, mp. 61°C.

Mass:m/e: 186 (M^+), 171 (M^+-CH_3) base peak.

LIII. Reaction of 3-allyl-3,4-dihydro-4-oxoquinazoline(6)with Trimethylsilyl chloride: Preparation of the O-Trimethyl silyl salt 51

Under stirring ice-cooling and protection from moisture trimethylsilyl chloride (10 ml excess) was added to a solution

of 6 (3 g, 20.5 m mol) in dry ether (200 ml), the reaction mixture left stirred for 2 hr, filtered, washed with dry ether (3 x 25 ml), and dried in vacuo to give 4.7 g (99%) of 51 as a white crystalline solid, mp. 160°C.

Mass:m/e: 186 (M^+-Me_3SiCl).

ir : ν_{max}(KBr) cm^{-1}: 2600 (br) (salt), 1610, 1580, 1550 (C=C, C=N), 960, 900 (Si-O).

LIV. Reaction of the trimethyl silyl salt 51 with n-butyl-lithium: Isolation of 2-n-Butyl-3-allyl-1,2,3,4-tetrahydro-4-oxoquinazoline(52)and 2-n-Pentylidineamino-N-allyl benzamide(53)

Under nitrogen, stirring and ice-cooling a solution of the trimethyl silyl salt 57 (4.5 g, 15 m mol) in dry ether (100 ml) was added to 0.9M ethereal n-butyl lithium (18 ml, 16 m mol). The reaction mixture left stirred for 1 hr, poured over saturated NH_4Cl, extracted with ethyl acetate, dried ($MgSO_4$), solvents evaporated in vacuo, and the residue chromatographed on silicagel. Elution with benzene:ethyl acetate::9:1 gave 0.615 g (16.5%) of 52 as a thick viscous liquid, bp. 160°C/0.2 mm.

Further elution with benzene:ethyl acetate (9:1) gave 0.650 g (17.45%) of 53 as a viscous liquid, bp. 190°C/0.2 mm.

52: ir : ν_{max}(neat) cm^{-1}: 3340 (NH), 2960, 2920, 2860 (saturated C-H), 1690 , (amide carbonyl), 1650, 1580 (C=C).

nmr: δ($CDCl_3$) 60 MHz: 0.8-1.9 (m, 9H, butyl), 4.0 (m, 2H, N-CH_2-), 5.2 (m, 2H, -CH=CH_2), 5.6-6.2 (m, 2H, CH=CH_2, CH-n-butyl), 7-7.6 (m, 4H, aromatic).

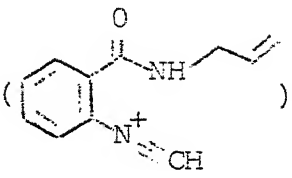
53: ir : ν_{max}(neat) cm^{-1}: 3320 (NH), 2960, 2930, 2860 (sat. CH), 1640 (br), (amide carbonyl).

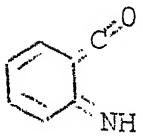
nmr: δ($CDCl_3$) 60 MHz: 0.8-1.9 (m, 9H, n-butyl), 4.5 (m, 2H, -NH-CH_2), 5.2 (m, 2H, -CH=CH_2), 5.9 (m, 1H, -CH=CH_2), 6.4-8.0 (m, 6H, aromatic, -N=CH-, -CO-NH-).

LV . Reaction of 3-Allyl-3,4-dihydro-4-oxoquinazoline (6) with Phenyllithium: Isolation of 2-Phenyl-3-allyl-1,2,3,4-tetrahydro-4-oxoquinazoline (54) and 2-Amino-N-allyl-benzamide(55)

Under nitrogen, stirring and ice-cooling 0.6M, ethereal PhLi, (20 ml, 12 m mol) was added in drops to a solution of 6 (1.86 g, 10 m mol) in dry ether (50 ml). The reaction mixture was left stirred overnight, poured over saturated NH_4Cl solution, extracted with ether, dried ($MgSO_4$) and chromatographed on silica-gel. Elution with benzene:ethyl acetate::9:1 gave 1.0 g (35%) of 54, mp. 129-30°C.

Elution with benzene:ethyl acetate::4:1 gave 0.2 g (8.3%) of 55, mp. 95-7°C (lit.[65] mp. 92-3°C).

54: Mass:m/e: 264 (M^+), 223 (M^+-CH_2), 187 (),

119 ()$^+$.

Anal. Calcd for $C_{17}H_{16}N_2O$ (Mol. Wt. 264).

C, 77.27; H, 6.06%

Found C, 77.27; H, 6.06%

ir : ν_{max}(KBr) cm^{-1}: 3300 (NH), 1630 (amide carbonyl).

nmr: $\delta(CDCl_3)$ 60 MHz: 4.5-5.2 (m, 4H, -N-C<u>H</u>$_2$-, -CH=C<u>H</u>$_2$), 5.65 (d, 1H, -N-C<u>H</u>-Ø), 6.4 (m, 1H, 6'-quinazoline ring), 6.75 (m , 1H, 6'-quinazoline ring), 7.0 (d, 1H, 7'-quinazoline ring), 7.2 (s, 5H, phenyl), 7.8 (d, 1H, 5'-quinazoline ring).

55: Mass:m/e: 176 (M^+), 120 (M^+- .HN ), 92 (M^+-.HN-CO).

ir : ν_{max}(KBr) cm^{-1}: 3440, 3320 (NH), 1640 (amide carbonyl), 1620, 1590 (C=C).

nmr: $\delta(CDCl_3)$ 60 MHz: 4.0 (m, 2H, -N-C<u>H</u>$_2$-), 5.2 (m, 2H, -CH=C<u>H</u>$_2$), 6.0 (m, 1H, -C<u>H</u>=CH$_2$), 6.3-7.3 (m, 4H, aromatic).

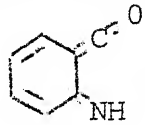
LVI . Themolysis of 54: Transformation to 55

A solution of 54 (0.5 g, 1.9 m mol) in xylene (5 ml) was refluxed for 2 hr, solvents evaporated and the residue chromatographed on silica gel. Elution with benzene:ethyl acetate::1:1, followed by crystallisation from benzene:hexane::2:1 gave 0.3 g (90%) of 55, mp. 95-7°C, whose properties were identical to that obtained from experiment LV .

LVII . Reaction of 3-(2'-Hydroxyethyl)-3,4-dihydro-4-oxoquinazoline(17) with Phenyllithium : Isolation of 2-Phenyl-3-(2'-hydroxyethyl)-1,2,3,4-tetrahydro-4-oxaquinazoline(56)

Under nitrogen, stirring and ice-cooling PhLi (1.6g, 19.5 m mol) in ether (35 ml) was added in drops to a solution of 17 (3.0g, 16.0 m mol) in dry THF (100 ml). The reaction mixture was left stirred for 5 hr, poured over saturated NH_4Cl solution, extracted with THF (2 x 100 ml), dried ($MgSO_4$), solvents evaporated and the residue chromatographed on silica gel. Elution with benzene:ethyl acetate::2:3 gave 0.723g (33.6%) of 56, mp. 115-6°C.

Further elution with benzene:ethyl acetate::3:7 gave 1.456g (48.53%) of unreacted 17.

Mass:m/e: 268 (M^+), 208(M^+-.HN-CH_2-CH_2-OH), 191 (M^+- .C_6H_5), 119 ().

Anal. Calcd for $C_{16}H_{16}N_2O_2$ (Mol. Wt. 268).
C, 71.64; H, 5.97; N, 10.44%
Found C, 71.8 ; H, 6.22; N, 10.81%

ir : ν_{max}(KBr) cm^{-1}: 3400 (OH), 3320 (NH), 1620, 1610, 1580 (C=O).

nmr: $\delta(CDCl_3)$ 60 MHz: 3.1 (m, 2H, -N-CH_2-), 3.6 (m, 3H, -CH_2-OH), 4.8 (br, 1H, -NH-), 5.8 (d, 1H, 2'-quinazoline ring), 6.4 (m, 1H, 8'-quinazoline ring), 6.8 (m, 1H, 6'-quinazoline ring), 7.1 (m, 1H, 7'-quinazoline ring), 7.3 (s, 5H, phenyl), 7.85 (dd, 1H, 5'-quinazoline ring).

LVIII. Hydrolysis of 56 with 2N NaOH: Isolation of anthranilic acid(1)

A suspension of 56 (0.097g, 0.36 m mol) in 2N NaOH (10 ml, excess) was refluxed for 5 hr, cooled, admixed with 2N HCl to pH 3, extracted with CH_2Cl_2, dried ($MgSO_4$) and evaporated to give 0.043g (84.2%) of 1, whose properties were found to be identical to an authentic sample.

LIX. Reaction of 3-(2'-Hydroxyethyl)-4-oxoquinazoline(17) with n-butyl lithium: Isolation of 2-Butyl-3-(2'-hydroxyethyl)-1,2,3,4-tetrahydro-4-oxoquinazoline(57)

Under nitrogen, stirring and ice-cooling, n-BuLi (1.12g,

33.0 m mol) in ether (60 ml) was added in drops over 1 hr, to a solution of 17 (3.0g, 16.0 m mol) in dry THF (50 ml), poured over saturated NH_4Cl solution, extracted with ethyl acetate, dried ($MgSO_4$), solvents evaporated and the residue chromatographed on silica gel. Elution with benzene:ethyl acetate::2:3 gave 0.787g (42.64%) of 57 as a while crystalline solid, mp.94-5°C.

Further elution with benzene:ethyl acetate::3:7 gave 1.587g (52.9%) of unreacted 17.

57: Anal. Calcd for $C_{14}H_{20}N_2O_2$ (Mol. Wt. 248).
C, 67.74; H, 8.06; N, 11.29%
Found C, 68.03; H, 7.76; N, 11.32%

ir : ν_{max}(KBr) cm^{-1}: 3300 (br, OH, NH), 2950, 2800 (sat. CH), 1630, 1570, (C=O).

nmr: δ ($CDCl_3$) 500 MHz: 0.86 (t, 3H, $-CH_3$), 1.25 (m, 4H, $-CH_2-CH_2-CH_3$), 1.65, 1.85 (m, m, 2H, $-CH-CH_2-$), 3.18 (br, 1H, $-CH_2-OH$), 3.63 (br, 1H, $-NH-CH_2-$), 4.65 (m, 2H, $-CH_2-OH$), 6.65 (d, 1H, 8'-quinazoline ring), 6.84 (t, 1H, 6'-quinazoline ring), 7.25 (m, 1H, 7'-quinazoline ring), 7.85 (d, 1H, 5'-quinazoline ring), 3.8 (m, 2H, $N-CH_2-CH_2-$), 4.0 (m, 1H, 2'-quinazoline ring).

LX . Reaction of 3-(2'-Aminoethyl)-3,4-dihydro-4-oxoquinazoline (24) with Lithium di-n-butylamide: Isolation of 2-(Di-n-butyl-aminomethenyl) amino-N-(2'-anilinoethyl) benzamide(58)

Under nitrogen, stirring and ice-cooling, a solution of 24 (0.9g, 3.4 m mol) in dry ether (25 ml) was added, in drops, over 0.5 hr to a solution of lithium di-n-butylamide prepared from di-n-butylamine (0.9g, 6.9 m mol) and butyllithium (0.44g, 6.5 m mol). The reaction mixture was left stirred overnight, poured over saturated NH_4Cl solution, extracted with ether, dried ($MgSO_4$), evaporated and the residue chromatographed on silica gel. Elution with benzene:ethyl acetate::4:1 gave 0.325g (26.1%) of 58, as a syrup.

ir : ν_{max}(neat) cm^{-1}: 3350 (NH), 2960, 2920, 2860 (sat. CH), 1670 (amide carbonyl).

nmr: δ($CDCl_3$+DMSO-d_6) 60 MHz: 0.6-1.7 (m, 14H, (-CH_2-CH_2--CH_3)x2), 3.2 (m, 6H, (-N-CH_2-)x2, -N-CH_2-CH_2-NH), 3.55 (t, 2H, -N-CH_2-CH_2-NH), 6.2-8.2 (m, 5H, aromatic, -N=CH-N-).

LXI . Reaction of 3-(2'-cyanoethyl)-3-4-dihydro-4-oxoquinazoline (26) with Phenyllithium: Isolation of 2-Phenyl-1,2,3,4-tatrahydro-4-oxoquinazoline(59) and 3,4-Dihydro-4-oxoquinazoline(2)

Under nitrogen, stirring and ice-cooling, a solution of PhLi (2.51g, 30 m mol) in ether (48 ml) was added in drops over

1.5 hr to a solution of 26 (3.0g, 15.0 m mol) in dry THF (50 ml). The reaction mixture was left stirred for 12 hr, poured over brine (100 ml), extracted with ethyl acetate (3x75 ml), dried ($MgSO_4$), evaporated and the residue chromatographed on silica gel. Elution with benzene:ethyl acetate::3:2 gave 0.625g (18.5%) of 59, mp. 228°C (lit.[66] mp. 228°C).

Further elution with benzene:ethyl acetate::1:1 gave 0.182g (6.06%) of unreacted 26.

Finally elution with benzene:ethyl acetate::1:4 gave 1.280g (65.46%) of 2, mp. 214°C (lit.[33] mp. 216°C).

59: Mass:m/e: 224 (M^+), 147 ($M^+ - .C_6H_5$), 120 ($M^+ - .C_6H_5$-HCN), 92 ($M^+ - .C_6H_5$-HCN-CO).

Anal. Calcd for $C_{14}H_{12}N_2O$ (Mol. Wt. 224).
C, 75.0; H, 5.36; N, 12.5%
Found C, 74.4; H, 5.67; N, 12.1%

ir : ν_{max}(KBr) cm^{-1}: 3300, 3200 (NH), 1670 (amide carbonyl), 1620, 1510 (C=C).

nmr: δ(DMSO-d_6) 500 MHz: 5.72 (m, 1H, -NH-CH-NH-), 6.5-7.65 (m, 10H, aromatic, NH-CH-Ph), 8.22 (d, 1H, -CO-NH-CH).

LXII . Hydrolysis of 3-Allyl-3,4-Dihydro-4-oxoquinazoline with 2N NaOH: Isolation of 2-Benzoylamino-N-allylbenzamide(60), 2-Phenyl-3,1 (4H)-benzoxazone (61) and Benzoylanthranilic acid (65)

A suspension of 6 (1.0g, 5.37 m mol) in 2N NaOH (10 ml, excess) was refluxed for 1.5 hr, ice-cooled, admixed with benzoyl chloride (4x0.4 ml) followed by 2N NaOH (4x2 ml), the mixture well mixed, extracted with ether, dried ($MgSO_4$), evaporated and the residue chromatographed on silica gel. Elution with benzene:hexane::1:1 gave 0.33g (27.5%) of 61, mp. 123-4°C (lit.[68] mp. 124°C), whose properties were identical to that of an authentic sample (Experiment LXIV).

Further elution with benzene:ethyl acetate::9:1 gave 0.28g (17%) of 60, mp. 95-6°C.

The aqueous layer was adjusted to pH 2-3 with conc. HCl, filtered, dried and crystallised from hexane:ethyl acetate::1:1 to give 0.602g (43%) of 65, mp. 181°C (lit.[71] mp. 181°C), whose properties were identical to that of an authentic sample (Experiment LXIII).

60: Mass:m/e: 280 (M^+), 224 (M^+- .HN ), 203 (M^+- .C_6H_5), 196 (M^+- .HN  -CO), 175 (M^+- .C_6H_5-CO).

Anal. Calcd for $C_{17}H_{16}N_2O_2$ (Mol. Wt. 280).

C, 72.8; H, 5.71%

Found C, 72.83; H, 5.44%

ir : ν_{max}(KBr) cm^{-1}: 3360 (NH), 1650 (amide carbonyl), 1600, 1590, 1520 (C=C, secondary amide).

nmr: δ($CDCl_3$) 200 MHz: 4.15 (t, 2H, -N-C<u>H</u>$_2$-), 5.3 (m, 2H, -CH=C<u>H</u>$_2$), 5.95 (m, 1H, -C<u>H</u>=CH$_2$), 6.7 (s, br, 1H, -CO-<u>NH</u>-CH$_2$-), 7.1 (t, 1H, 5'-anthranilic acid), 7.35 (m 6H, 3,4,5-phenyl) , 3',4'-anthranilic acid, -N<u>H</u>-CO-Ø), 8.1 (d,d, 2H, 2,6-phenyl) , 8.7 (d, 1H, 6'-anthranilic acid).

<u>61</u>: ir : ν_{max}(KBr) cm^{-1}: 1760 (lactone), 1610, 1565 (C=C, C=N).

nmr: δ ($CDCl_3$) 200 MHz: 7.55 (q, 4H, 2,3,5,6-phenyl), 7.75 (d, 1H, 4-phenyl), 7.85 (qd, 1H, 8'-benzoxazone ring), 8.25 (dd, 1H, 5'-benzoxazone ring), 8.35 (qd, 2H, 6',7'-benzoxazone ring).

LXIII. <u>Preparation of an authentic sample of Benzoylanthranilic acid (65)</u>

Under vigorous mixing and ice-cooling, benzoyl chloride (1.4g, 10 ml) was added to a solution of anthranilic acid (1.37g, 10 m mol) in 2N NaOH (10.0 ml, excess), the resulting clear solution adjusted to pH 3 with conc. HCl, filtered, washed with

water, dried and crystallised from benzene:ethyl acetate::1:1 to give 2.501g (85%) of 65, mp. 181°C, whose properties were identical to that obtained from Experimental LXII .

LXIV. Preparation of an authentic sample of 2-Phenyl-3,1 (4H) benzoxazone[68] (61)

A mixture of N-Benzoylanthranilic acid (0.05g, 0.21 m mol) and acetic anhydride (0.2g, 2.0 m mol) was refluxed for 1.5 hr, excess acetic anhydride removed in vacuo, the residue admixed with dry methanol, solvents evaporated in vacuo, the residue triturated with ice-cold methanol, filtered and crystallised from hot methanol to give 0.035g (76%) of 61, mp. 123°C, whose properties were identical to that obtained from Experiment LXII .

LXV. Hydrolysis of 2-Benzoylamino-N-allylbenzamide(60)with 2N NaOH: Isolation of Anthranilic acid(1)

A mixture of 60 (0.14g, 0.5 m mol) and 2N NaOH (5 ml, 10 m mol) was refluxed for 1.5 hr, during which the starting material was consumed (tlc). The reaction mixture was cooled to 0°C, adjusted to pH 3 with conc. HCl, extracted with ethyl acetate, dried ($MgSO_4$) and evaporated to give 0.061g (90%) of anthranilic acid, mp. 145°C.

LXVI . Preparation of N-Formylanthranilic acid[69] (62)

A mixture of anthranilic acid (13.7g, 100 m mol) and formic acid (80%) (15.8g, 344 m mol) was refluxed for 3.5 hr, filtered, powdered, washed with benzene (3x50 ml) and crystallised from hot benzene to give 14.6g (88.5%) of 62, mp. 164-5°C (lit. mp.[69] 169°C).

LXVII . Hydrolysis of N-Formylanthranilic acid 62 with 2N NaOH: Isolation of(1)

A mixture of N-Formylanthranilic acid 62 (2.0g, 12,2 m mol) and 2N NaOH (30 ml, 60 m mol) was refluxed for 2.5 hr, cooled in ice, pH adjusted to 3 with conc. HCl, extracted with ethyl acetate, dried ($MgSO_4$) and evaporated to give (1.412g, 86.3%) of anthranilic acid (1), mp. 145°C.

LXIII. Hydrolysis of 6-Nitro-3-allyl-3,4-dihydro-4-oxoquinazoline (14) with 0.5N NaOH: Isolation of 5-Nitroanthranilic acid(63)

A mixture of 14 (3.0g, 13 m mol) in 0.5N NaOH (100 ml, 50 m mol) was refluxed for 2 hr, cooled, the preceipitated 5-Nitro anthranilic acid (63) was filtered, washed with cold water and dried. The filtrate was adjusted to pH 3 with conc. HCl, filtered, washed and dried to give a second batch of 63. The resulting filtrate was extracted with ethyl acetate dried ($MgSO_4$)

and evaporated to give a third batch of 63. All the three lots were found to be identical to give a combined yield of 1.816g (95%) of 5-Nitro anthranilic acid (63) mp. 274°C (lit.[73] mp.275-6°C).

LXIX. Hydrolysis of 3-(2'-Diethoxyethyl)-3,4-dihydro-4-oxoquinazoline (8) with 2N NaOH: Isolation of 1-Amino-2',2'-diethoxy ethane as the benzoyl derivative (64) and N-Benzoyl anthranilic acid(65)

A mixture of 8 (5.0g, 19 m mol) and 2N NaOH (80 ml, 160 m mol) was refluxed for 12 hr, the reaction mixture cooled, admixed with benzoyl chloride (5.9g, 42 m mol), vigorously mixed, extracted with ethyl acetate, dried ($MgSO_4$), evaporated and the residue chromatographed on silica gel. Elution with benzene:ethyl acetate::4:1 gave 3.73g (82.5%) of 64 as a thick viscous liquid, bp. 115°C/0.25 mm.

The aqueous layer was adjusted to pH 3 with conc. HCl, filtered, washed with water, dried and crystallised from hexane: ethyl acetate::1:1 to give 2.625g (57.2%) of 65, mp. 181°C whose properties were identical to that obtained from Experiment LXIII.

64: Mass:m/e: 191 ($M^+-C_2H_5OH$).

Anal. Calcd for $C_{13}H_{19}NO_3$ (Mol. Wt. 237).

C, 65.82; H, 8.01%

Found C, 65.54; H, 7.8 %

ir : ν_{max}(neat) cm^{-1}: 3345 (NH), 1660 (amide carbonyl), 1605, 1580, 1550 (C=C, secondary amide).

nmr: $\delta(CDCl_3)$ 60 MHz: 1.15 (t, 6H, $(-CH_2-\underline{CH_3})$x2), 3.5 (m, 6H, $(-\underline{CH_2}-CH_3)$x2, $-NH-\underline{CH_2}-$), 4.55 (t, 1H, $-CH_2-\underline{CH}-$), 6.55 (br, 1H, $-CO-\underline{NH}-$), 7.1-7.8 (m, 5H, aromatic).

LXX . Hydrolysis of 6-Nitro-3-(2'-diethoxyethyl)-3,4-dihydro-4-oxoquinazoline (15) followed by benzoylation: Isolation of 5-Nitro-N-benzoyl anthranilic acid (63a) and 1-Benzoylamino-2,2-diethoxyethane (64)

A mixture of 15 (3.0g, 11.4 m mol) and 2N NaOH (50 ml, 100 m mol) was refluxed for 2.5 hr, cooled, admixed with benzoyl chloride (3.54g, 25.2 m mol), vigorously mixed, extracted with ethyl acetate, dried ($MgSO_4$), solvents evaporated, and the residue chromatographed on silica gel. Elution with benzene: ethyl acetate::4:1 gave 2.58g, (86.4%) of 64, bp. 115°/0.25 mm, whose properties were identical to that obtained in ExperimentLXIX.

The aqueous layer was adjusted to pH 3 with conc. HCl, filtered, washed with water and air dried. The filtrate was extracted with ethyl acetate, dried ($MgSO_4$) and evaporated to give a second lot of 63a. The combined lots on crystallisation from hot ethyl acetate gave 2.422g (77.6%) of 63a, mp. 255°C (lit.[71] mp. 257-8°C).

LXXI. Hydrolysis of 3-(2'-Nitroethyl)-3,4-dihydro-4-oxoquinazoline (19) with 2N NaOH followed by benzoylation: Isolation of 2-Phenyl-3,1(4H)benzoxazone (61)

A mixture of 19 (1.0g, 5.56 m mol) and 2N NaOH (10 ml, 20 m mol) was refluxed for 2 hr, cooled admixed under vigorous shaking with benzoyl chloride (1.92g, 13.7 m mol), adjusted to pH 3 with conc. HCl, extracted with benzene, dried ($MgSO_4$), evaporated and the residue chromatographed on silica gel. Elution with benzene:hexane::1:1 gave 0.622g (61.1%) of 61, which was crystallised from hot hexane, mp. 123-4°C (lit.[68] mp. 124°C) which was identical to that obtained from Experiment LXIV.

LXXII. Hydrolysis of 3-Benzoylamino-3,4-dihydro-4-oxoquinazoline (31) with 2N NaOH: Isolation of O-Aminobenzoyl hydrazine (66) 1-Benzoyl-2-o-aminobenzoyl hydrazine (67) and Anthranilic acid (1)

A solution of 31 (5.0g, 21.3 m mol) in 2N NaOH (100 ml, 200 m mol) was refluxed for 16 hr, cooled, extracted with ethyl acetate (250 ml) dried ($MgSO_4$) and concentrated ($\sim$10 ml), cooled and filtered to give 0.126g (4.54%) of 67 as white crystalline solid, mp. 178°C.

The filtrate was further concentrated ($\sim$2 ml) and chromatographed on silica gel. Elution with benzene:ethyl acetate::7:3 gave additional quantity of 0.1g (3.6%) of 67.

Further elution with benzene:ethyl acetate::1:4 gave 0.294g (17.9%) of 66 as white crystals, mp. 123°C (lit.[72] mp. 121°C).

The aqueous layer was adjusted to pH 3 with conc. HCl, washed with ice-water, dried extracted with ethyl acetate and the residue on crystallisation from hot ethyl acetate gave 2.11g (42.2%) of unchanged 31, mp. 189°C.

The ethyl acetate extract on evaporation gave 1.086g (73%) of anthranilic acid (1), mp. 146°C.

66: ir : ν_{max}(KBr) cm^{-1}: 3440, 3320 (NH_2), 1650 (amide carbonyl), 1620, 1580 (C=C).

nmr: δ(DMSO-d_6) 500 MHz: 6.22 (s, 4H, -CO-NH-$\underline{NH_2}$, -C_6H_4-$\underline{NH_2}$), 6.4 (t, 1H, 5'-anthranilic acid), 6.62 (d, 1H, 3'-anthranilic acid), 7.05 (t, 1H, 4'-anthranilic acid), 7.73 (d, 1H, 6'-anthranilic acid), 9.4 (s, 1H, -CO-$\underline{NH}$).

67: Mass:m/e: 255 (M^+).

Anal. Calcd for $C_{14}H_{14}N_3O_2$ (Mol. Wt. 255)
C, 65.88; H, 5.1 %

Found C, 65.50; H, 5.37%

ir : ν_{max}(KBr) cm^{-1}: 3400, 3280 (br)(NH_2), 1650 (amide carbonyl), 1620, 1575 (C=C).

nmr: δ(DMSO-d_6) 500 MHz: 6.3 (s, 2H, -$\underline{NH_2}$), 6.42 (t, 1H, 5'-anthranilic acid), 6.65 (d, 1H, 3'-anthranilic acid).

7.18 (t, 1H, 4'-anthranilic acid), 7.48 (t, 2H, 3,5-phenyl), 7.55 (d, 1H, 4-phenyl), 7.6 (d, 1H, 6'-anthranilic acid), 7.9 (d, 2H, 2,6-phenyl), 10.2 (br, 2H, -NH-NH-).

LXXIII. Reaction of Methylanthranilate with Hydrazine: Preparation of o-Aminobenzoyl hydrazine(66)

A mixture of methylanthranilate (0.5g, 3.3 m mol) and hydrazine hydrate (100%) (1ml, excess) was refluxed for 5 hr, excess hydrazine removed in vacuo and the residue on crystallisation from benzene:hexane::1:1 gave 6.389g (77.8%) of 66, mp. 124°C whose properties were identical to that obtained from Experiment LXXII.

LXXIV. Establishment of the intermediacy of 67 in the 31 $\longrightarrow$ 1 change: Reaction of 1-Benzoyl-2-o-aminobenzoylhydrazine(67) with 2N NaOH: Isolation of anthranilic acid (1)

A mixture of 67 (0.1g, 0.3 m mol) and 2N NaOH (10 ml, 20 m mol) was refluxed for 3 hr, cooled, adjusted to pH 3 with conc. HCl, estracted with ethyl acetate, dried ($MgSO_4$) and solvents evaporated to give 0.04g (75%) of 1.

LXXV. Regioselective alkylation of Adenine (68): Preparation of 9-Benzyladenine[61] (69)

Under vigorous stirring and protection from moisture, benzyl bromide (1.438g, 8.41 m mol) was added over 0.25 hr to a suspension of the sodium salt of adenine - prepared by reaction of NaH (0.25g, 18.4 m mol) during 2 hr with adenine (1.0g, 7.4 m mol) in dry DMF (25 ml). The mixture was left stirred for 16 hr, cooled in ice, filtered, washed with methanol, dried *in vacuo* and crystallised from hot methanol to give 0.435g (26.1%) of 9-benzyladenine (69), mp. 234-5°C (lit.[61] mp. 235°C).

nmr: δ(DMSO-d_6) 100 MHz: 5.4 (s, 2H, -CH_2-Ø), 7.3 (m, 5H, phenyl), 8 (s,s, 1H, 1H, 2',8'-purine ring).

LXXVI. Benzylation of 69: Preparation of 1,9-Dibenzyladenine(70)

Under stirring and protection from moisture, benzyl bromide (0.4 ml, 3 m mol) was added to a solution of 9-Benzyladenine (0.5g, 2 m mol) in dry DMF (20 ml), left stirred for 12 hr, solvents evaporated *in vacuo*, the residue dissolved in minimum amount of methylene chloride, treated with a few drops of dry ether to initiate crystallisation, filtered, washed with CH_2Cl_2:ether::1:1 (2x5 ml) and recrystallised from methanol to give 0.5g (71.4%) of 70, mp. 155-65°C (lit.[62] mp. 163-72°C).

Mass:m/e: 315 (M^+), 224 ($M^+-C_6H_5-CH_2^\cdot$), 197 ($M^+-C_6H_5-CH_2^\cdot-HCN$), 106 ($M^+-2C_6H_5-CH_2^\cdot-HCN$).

ir : ν_{max}(KBr) cm^{-1}: 3400 (br)(NH), 1670 (C=NH), 1620, 1575, 1520 (C=C, C=N).

nmr: δ(DMSO-d_6) 200 MHz: 2.25 (s, 1H, =NH), 5.45 (d, 4H, $-CH_2-C_6H_5$x2), 7.3 (m, 10H, phenylx2), 8.45, 8.65 (s, s, 1H, 1H, purine ring).

LXXVII. Reaction of 9-Benzyladenine (69) with 1-Bromo-2-hydroxy ethane: Isolation of 1-(2'-Hydroxyethyl)-9-Benzyl-6-iminopurine (71)

Under stirring, 1-Bromo-2-hydroxy ethane (1.89g, 1.51 m mol) was added to a solution of 9-Benzyladenine (0.34g, 1.51 m mol) in dry DMF (20 ml) held at 60°C. The reaction mixture was left stirred at 110-20°C for 24 hr, solvents evaporated *in vacuo*, the residue dissolved in minimum amount of hot methanol, cooled to 0°C, filtered washed with ice-cold methanol:ether::2:1, dried *in vacuo* and crystallised from methanol:ether::2:1 to give, 0.2g (49.26%) of 71, mp. 252°C.

Mass:m/e: 251 (M^+-H_2O).

ir : ν_{max}(KBr) cm^{-1}: 3400 (br)OH, 3340 (NH), 1680 (C=NH).

nmr: δ(DMSO-d_6) 500 MHz: 3.75 (br, 2H, $-N-CH_2-$), 4.45 (br, 2H, $-O-CH_2-$), 5.55 (s, 2H, $-CH_2-Ø$), 7.4 (s, 5H, phenyl), 8.6, 8.7 (s, s, 1H, 1H, purine ring).

LXXVIII. Benzylation of 9-Benzylhypoxanlhine (43): Preparation of 1,9-Dibenzyl-6-oxopurine (72)

Under stirring and protection from moisture, benzyl bromide (0.171g, 1.2 m mol) followed by freshly ignited and cooled K_2CO_3 (0.13g, 1.2 m mol) was added to a suspension of 43 (0.226g, 1 m mol) in dry DMSO (5 ml). The reaction mixture was left stirred for 12 hr, filtered, the filtrate poured over crushed ice, the separated solid filtered, washed with ice-cold water (3x100 ml) air dried at 90-100°C and crystallised from hot ethyl acetate to give 0.235g (74.36%) of 72, mp. 205°C (lit.[59] mp. 208°C).

LXXIX. Reaction of 9-Benzylhypoxanthine (43) with 1-Bromo-2-hydroxy ethane : Isolation of 1-(2'-Hydroxyethyl)-9-benzyl-6-oxopurine (73)

1-Bromo-2-hydroxyethane (0.725g, 6 m mol) was added to a stirred suspension of the sodium salt of 9-Benzylhypoxanthine - prepared from 43 (0.9g, 3.98 m mol) and NaOMe (6.08 m mol) in dry methanol (50 ml) - refluxed for 8 hr, solvents evaporated in vacuo the residue dissolved in minimum amount of water, adjusted to pH 7 with conc. HCl, filtered, washed with ice-cold water, dried and crystallised from methanol to give 0.353g (42.6%) of 73, mp. 172°C.

The methanol extract on evaporation gave unreacted 43, 0.207g (23%).

Anal. Calcd for $C_{14}H_{14}N_4O_2$ (Mol. Wt. 270)

C, 62.22; H, 5.18%

Found C, 61.55; H, 5.33%

ir : ν_{max}(KBr) cm^{-1}: 3400(br)(OH), 1700 (amide carbonyl), 1600, 1570, 1550 (C=C, C=N).

LXXX. Reaction of 4-Chloroquinazoline (4) with Acetoxime: Isolation of oxime ether 74

Under stirring and at 0°C, 4-chloroquinazoline (4) (2.0g, 12.1 m mol) was added to a solution of the sodium salt of acetoxime - prepared by mixing ice-cold saturated solutions of acetoxime (1.0g, 13.7 m mol) and sodium hydroxide (0.6g, 15 m mol) - left stirred for 3 hr, extracted with ether, dried ($MgSO_4$) and solvent evaporated to give 2.2g (90%) of 74 as a viscous liquid.

Anal. Calcd for $C_{11}H_{11}N_3O$ (Mol. Wt. 201)

C, 70.96; H, 5.37; N, 15.07%

Found C, 71.0 ; H, 5.21; N, 15.1 %

ir : ν_{max}(neat) cm^{-1}: 1620, 1570 (C=C, C=N).

nmr: $\delta(CDCl_3)$ 60 MHz: 1.95 (s, 6H, $-N=C(CH_3)_2$, 7.1-8.0 (m, 4H, 5',6',7',8'-quinazoline ring), 8.66 (s, 1H, 2'-quinazoline ring).

LXXXI. Pyrolysis of oxime ether 74: Isolation of 75

Under nitrogen, the oxime ether 74 (1.0g, 4 m mol) was held at 160°C for 6 hr, extracted with methylene chloride, solvents evaporated and the residue on preparative tlc with EtOAc as developer gave 0.259g (20%) of 75, mp. 205°C.

Mass:m/e: 161 (M^+)

ir : ν_{max}(KBr) cm^{-1}: 3340 (br), (OH,NH), 1685 (C=N-OH), 1585, 1560, 1520 (C=C, C=N).

nmr: δ (DMSO-d_6) 500 MHz: 7.48 (m, 1H), 7.63 (t, 1H), 7.76 (m, 2H), 8.1 (m, 2H), 8.32 (s, 1H).

LXXXII. Reaction of 4-Chloroquinazoline (4) with hydrazinehydrate (100%): Preparation of 4-Hydrazinoquinazoline[73] (76)

Under stirring and at 0°C, a mixture of 4 (1.0g, 6.08 m mol) and hydrazine hydrate (100%) (10 ml, excess) was left stirred overnight, filtered, washed with chilled methanol (3x5 ml) and crystallised from pyridine to give 0.78g (80%) of 76 as pale yellow needles, mp. 185-6°C (lit.[73] mp. 188-9°C).

ir : ν_{max}(KBr) cm^{-1}: 3320, 3200 (NH_2),1640, 1620, 1580 (C=C, C=N).

LXXXIII. Reaction of 76 with acetone: Preparation of 4-Isopropylidine hydrazinoquinazoline[74] (77)

A solution of 76 (1.0g, 6.25 m mol) in acetone:ethanol (4:1, 25 ml) was refluxed for 6 hr, solvents evaporated *in vacuo*, the residue triturated with dry ether, decanted, evaporated *in vacuo* and crystallised from benzene:ethyl acetate::1:1 to give 1.18g (95%) of 77 as pale yellow needles, mp. 174-5°C (lit.[74] mp. 177°C).

Tlc: ethyl acetate: Rf: 0.6

ir : ν_{max}(KBr) cm^{-1}: 3100 (NH), 1615, 1560 (C=C, C=N).

LXXXIV. Attempted Fischer-Indole cyclisation of 77 with PPA: Isolation of 2,4-Bis-O-aminophenyl-1,2,4-triazine (78) and 3,4-Dihydro-4-oxoquinazoline (2)

An intimate mixture of 77 (2.5g, 12.5 m mol) and PPA (20.0g, excess) was heated gradually to 160°C in 0.5 hr and held at 190°C for 3 hr. The reaction mixture was cooled, admixed with water (200 ml), adjusted to pH 7-8 with saturated Na_2CO_3 solution, extracted with CH_2Cl_2, dried ($MgSO_4$), solvents evaporated and the residue chromatographed on silica gel. Elution with benzene:ethyl acetate::7:3 gave 0.21g (9.65%) of the triazole 78, as fine while needles, mp. 205-6°C.

Further elution with benzene:ethyl acetate::2:3 gave unchanged 77 (1.05g, 42%) and with benzene:ethyl acetate::1:4 gave 3,4-Dihydro-4-oxoquinazoline (2), 0.425g (38.8%) mp. 212.

78: Mass:m/e: 251 (M^+)

Anal. Calcd for $C_{14}H_{13}N_5$ (Mol. Wt. 251)
C, 66.93; H, 5.18%
Found C, 67.9 ; H, 5.32%

ir : ν_{max}(KBr) cm^{-1}: 3460, 3400, 3340 (NH_2), 1610, 1575, 1550 (C=C, C=N).

nmr: δ(DMSO-d_6) 500 MHz: 6.64 (t, 2H, 5'-ring), 6.81 (d, 2H, 3'-ring), 7.14 (t, 2H, 4'-ring), 7.83 (br, 2H, 6'-ring).

LXXXV. Reaction of 9-Benzyl-6-chloropurine 36 with acetoxime: Preparation of oxime ether 79

Under stirring, 36 (0.5g, 2.05 m mol) was added during 0.25 hr to a solution of the sodium salt of acetoxime - prepared from mixing concentrated ice-cold aqueous solutions of acetoxime (0.224g, 3.1 m mol) and NaOH (0.122g, 3.3 m mol), left stirred for 20 hr, filtered, washed with distilled water (3x50 ml) and dried in vacuo to give 0.345g (61.6%) of 79, mp. 170°C.

Anal. Calcd for $C_{15}H_{15}N_4O$ (Mol. Wt. 281)

C, 64.05; H, 5.34; N, 24.91%

Found C, 64.03; H, 5.23; N, 24.64%

ir : ν_{max}(KBr) cm^{-1}: 1590, 1570 (C=C, C=N), 1060 (C-O).

nmr: $\delta(CDCl_3)$ 60 MHz: 2.2 (d, 2H, $-N=C(C\underline{H}_3)_2$), 5.4 (s, 2H, $-C\underline{H}_2-\emptyset$), 7.3 (s, 5H, phenyl), 7.9 (s, 1H, 8'-purine ring), 8.7 (s, 1H, 2'-purine ring).

LXXXVI. Attempted thermal cyclisation of 79

Attempted cyclisation of 79, either neat at 180°C or in refluxing O-dichlorobenzene gave intractable mixtures.

LXXXVII. Reaction of 7-Benzyl-6-chloropurine(37) with acetoxime: Preparation of oxime ether 80

Under stirring 37 (1.3g, 5.3 m mol) was added to a solution of the sodium salt of acetoxime - prepared from mixing ice-cold, aqueous, saturated solutions of acetoxime (0.582g, 7.9 m mol) and NaOH (0.317g, 7.9 m mol) - left stirred for 20 hr, filtered, washed with distilled water (3x20 ml), dried *in vacuo* and crystallised from benzene:ethyl acetate::1:1 to give 0.85g (59.8%) of 80, mp. 155°C.

Anal. Calcd for $C_{15}H_{15}N_5O$ (Mol. Wt. 267)

C, 64.05; H, 5.34; N, 24.91%

Found C, 64.12; H, 5.38; N, 25.12%

ir : ν_{max}(KBr) cm^{-1}: 1610, 1545 (C=C, C=N), 1040 (C-O).

nmr: δ($CDCl_3$) 60 MHz: 1.9, 2.1 (s, s, 3H, 3H, $-N=C(\underline{CH_3})_2$), 5.6 (s, 2H, $-\underline{CH_2}-\emptyset$), 7.1 (m, 5H, phenyl), 8.0 (s, 1H, 8'-purine ring), 8.6 (s, 1H, 2'-purine ring).

LXXXVIII. Attempted thermal cyclisation of 80

Under nitrogen, 80 (0.267g, 1 m mol) was held at 165°C for 4 hr. The dark residue consisted of a mixture of products (tlc) which was found intractable.

LXXXIX. Reaction of 9-Benzyl-6-chloropurine (36) with Hydrazine hydrate (100%): Preparation of 9-Benzyl-6-hydrazinopurine[54] (81)

A mixture of 36 (1.0g, 4.1 m mol) and hydrazine hydrate (100%) (10 ml, excess) was left stirred at 0°C for 0.5 hr, filtered, washed with n-butanol, dried *in vacuo* and crystallised from hot methanol to give 0.85g (86.6%) of 81, mp. 209°C (lit.[54] mp. 209-10°C).

Anal. Calcd for $C_{12}H_{12}N_6$ (Mol. Wt. 240)
C, 60.0 ; H, 4.65%
Found C, 59.64; H, 4.65%

XC. Reaction of 9-(2'-Tetrahydropyranyl)-6-chloropurine (41) with acetoxime: Preparation of oxime ether 82

Under stirring and ice-cooling 41 (2.0g, 8.35 m mol) was added to a solution of the sodium salt of acetoxime - prepared from mixing of ice-cold saturated solutions of acetoxime (0.915g, 12.5 m mol) and NaOH (0.5g, 12.5 m mol) - in 0.5 hr, left stirred for 0.5 hr, filtered, washed with ice-cold distilled water, dried *in vacuo* and crystallised from hot ethyl acetate to give 1.75g (75.9%) of 82, mp. 135°C.

Anal. Calcd for $C_{13}H_{17}N_5O_2$ (Mol. Wt. 275)
C, 56.72; H, 6.18%
Found C, 56.28; H, 5.98%

ir : ν_{max}(KBr) cm^{-1}: 2950, 2810 (saturated C-H), 1590, 1570, 1540 (C=C, C=N), 1050 (C-O).

nmr: $\delta(CDCl_3)$ 60 MHz: 1.9 (m, 6H, THP ring), 2.1, 2.2 (s, s, 3H, 3H, $-N=C(CH_3)_2$), 3.9 (m, 2H, $-O-CH_2-$), 5.6 (m, 1H, N-CH-O), 8.0 (s, 1H, 8'-purine ring), 8.5 (s, 1H, 2'-purine ring).

XCI. Attempted thermal cyclisation of 82: Isolation of 9-(2'-Tetrahydropyranyl)-6-oxopurine(83)

Under nitrogen, 82 (1.0g, 3.63 m mol) was held at 140°C for 1 hr. The dark residue was extracted with hot ethyl acetate,

solvents evaporated and the residue on preparative tlc using ethyl acetate as developer gave 0.11g (20.1%) of 82 as a white crystalline solid, mp. 198-200°C.

Mass:m/e: 220 (M^+)

Anal. Calcd for $C_{10}H_{12}N_4O_2$ (Mol. Wt. 220)

C, 54.5 ; H, 5.45%

Found C, 54.72; H, 5.59%

ir : ν_{max}(KBr) cm^{-1}: 3400 (NH), 1690 (amide carbonyl).

nmr: δ(DMSO-d_6) 200 MHz: 1.4-1.9 (m, 6H, THP ring), 3.75 (m, 2H, -O-C<u>H</u>$_2$-), 5.6 (m, 1H, -N-C<u>H</u>-O-), 8.1 (s, 1H, 8'-purine ring), 8.3 (s, 1H, 2'-purine ring).

XCII. Reaction of Anthranilic acid (1) with KCNO[76]:Preparation of 1,2,3,4-Tetrahydro-2,4-dioxoquinazoline[77](84)

Under stirring and ice-cooling a solution of potassium cyanate (15g, 185 m mol) in distilled water (50 ml) was added over 0.5 hr to a solution of anthranilic acid (20.0g, 146 m mol in AcOH:H_2O (11:700, 711 ml), prepared by warming. The resulting pasty mass was left stirred for 0.5 hr, admixed with solid NaOH (200g, 5000 m mol), maintaining the temperature below 40°C, left aside over night in the refrigerator, filtered, washed with ice-cold water (250 ml) and dried to give 25.5g (85.5%) of the disodium salt of 84, which was dissolved in water (1000 ml), held

at 90°C and under stirring treated with, in drops, H_2SO_4:H_2O::1:1 until acidic, cooled, filtered, washed with water (200 ml) and dried at 100°C to give 20.1g (85%) of 84, mp. > 360°C (lit.[77] mp. > 360°C).

XCIII. Reaction of 84 with $POCl_3$: Conversion of 2,4-Dioxoquinazoline to 2,4-Dichloroquinazoline (85)

A mixture of 84 (10.0g, 61.7 m mol) and $POCl_3$ (20 ml, 215 m mol) was held at 160°C for 16 hr, the hot solution poured over crushed ice (250g), filtered, pressed free of water, extracted with ether (350 ml) washed with 1N NaOH (2x100 ml), water (100 ml) dried ($MgSO_4$) and solvents evaporated to give 10.25g (83.4%) of 85, mp. 118°C (lit. mp.[78] 118°C).

XCIV. Reaction of 85 with Ethylene chlorohydrin: Preparation of 2-chloro-4-(2'-chloroethoxy)quinazoline[79] 86

Ethylene chlorohydrin (6.4g, 81.1 m mol) followed by freshly ignited K_2CO_3 (11.2g, 81.1 m mol) was added to a stirred solution of 85 (8.0g, 40.2 m mol) in dry acetone (120 ml). The reaction mixture was refluxed for 5 hr, cooled, filtered, solvents evaporated, the residue dried *in vacuo*, extracted with hot benzene and solvents evaporated to give 8.6g (87.6%) of 86, mp. 103°C (lit.[79] mp. 103°C).

ir : ν_{max}(KBr) cm^{-1}: 1610, 1570, 1550 (C=C, C=N), 1100 (C-O)

nmr: $\delta(CDCl_3)$ 60 MHz: 3.85 (t, 2H, $-O-\underline{CH_2}-$), 4.8 (t, 2H, $-\underline{CH_2}-Cl$), 7.2-7.85 (m, 3H, 6',7',8'-quinazoline ring), 8.1 (m, 1H, 5'-quinazoline ring).

XCV. Thermal rearrangement of 86: Preparation of 2-chloro-3-(2'-chloroethyl)-3,4-dihydro-4-oxoquinazoline[79] (87)

Compound 86 (6.0g, 24.8 m mol) on distillation at 176°/1.1 m gave 4.8g (80%) of 87, mp. 92°C (lit.[79] mp. 92°C).

ir : ν_{max}(KBr) cm^{-1}: 1680 (amide carbonyl), 1580, 1560 (C=C, C=N).

nmr: $\delta(CDCl_3)$ 60 MHz: 3.8 (t, 2H, $-N-\underline{CH_2}-$), 4.6 (t, 2H, $-\underline{CH_2}-Cl$), 7.2-7.9 (m, 3H, 6',7',8'-quinazoline ring), 8.1 (m, 1H, 5'-quinazoline ring).

XCVI. Reaction of 87 with Aniline: Preparation of 1-Phenyl-1,2,3,5-tetrahydro-5-oxoimidazo- [2,1-b] quinazoline(88)

Aniline (1.9g, 20 m mol) was added to a stirred solution of 87 (2.4g, 10 m mol) in absolute ethanol (25 ml). The reaction mixture was refluxed for 1.5 hr, cooled, filtered, washed with distilled water (3x10 ml) followed by ethanol (3x5 ml), dried and crystallised from hot benzene to give 2.1g (81.2%) of 88, mp.165° (lit.[80] mp. 165°C).

ir : ν_{max}(KBr) cm^{-1}: 1670 (amide carbonyl), 1620, 1580, 1550 (C=C, C=N).

nmr: δ($CDCl_3$)60 MHz: 3.85 (m, 4H, -N-CH_2-CH_2-N-), 7.2-8.3 (m, 9H, aromatic).

XCVII. Reduction of 88 with $NaBH_4/AlCl_3$: Isolation of 1-Phenyl-1,2,3,5-tetrahydroimidazo- [2,1-b] quinazoline (89)

A solution of the $AlCl_3$ complex of 88 - prepared by addition of $AlCl_3$ (0.66g, 5 m mol) over 0.5 hr to a stirred and cooled (0^oC) solution of 88 (1.31g, 5 m mol) in dry diglyme (125 ml) - was added in drops to a solution of $NaBH_4$ (0.95g, 25 m mol) in dry diglyme. The reaction mixture was left stirred at 85^oC for 1.5 hr, cooled to rt, admixed with water (30 ml) followed by conc. HCl ($\sim$0.5 ml), evaporated on a water bath, the residue was triturated with ethyl acetate, the organic extract discarded, the residue dissolved in water, made alkaline with NH_4OH, the white solid separated was filtered, washed with distilled water, dried and crystallised from benzene to give 1.1g (83.3%) of 89 as colourless prisms, mp. 188-90^oC.

Mass: m/e: 249 (M^+)

ir : ν_{max}(KBr) cm^{-1}: 1620, 1580, 1560 (C=C, C=N).

nmr: $\delta(CDCl_3)$ 60 MHz: 3.2 (m, 2H, $-C\underline{H}_2-CH_2-N-\emptyset$), 3.7 (m, 2H, $-CH_2-C\underline{H}_2-N-\emptyset$), 4.2 (s, 2H, 4'-quinazoline ring), 6.7-7.4 (m, 3H, 6',7',8'-quinazoline ring), 7.75 (dd, 1H, 5'-quinazoline ring).

XCVIII. Reaction of 88 with Phenyllithium: Isolation of 1,5-Diphenyl-1,2,3,5-tetrahydroimidazo- [2,1-b] quinazoline(9

Under stirring, nitrogen and ice-cooling 1.3M PhLi (0.8 ml, 1 m mol) was added to a solution of 88 (0.131g, 0.5 m mol) in dry THF (15 ml) during 0.25 hr, the mixture left stirred for 2 hr, poured over saturated NH_4Cl solution, extracted with CH_2Cl_2, drie ($MgSO_4$), evaporated, the residue successively washed with dry ether and hot dry benzene and crystallised from hot methanol to give 0.142g (87.7%) of 90, mp. 193-5°C.

Mass: m/e: 325 (M^+), 324 (M^+-H.).

ir : ν_{max}(KBr) cm^{-1}: 3030 (aromatic CH), 1630, 1570, (C=C).

nmr: $\delta(CDCl_3+DMSO-d_6)$ 90 MHz: 3.3 (m, 2H, 3'-ring), 3.75 (m, 2H, 2'-ring), 6.5-8.0 (m, 15H, 5'-ring, aromatic).

XCIX. Reaction of 88 with Trimethylsilyl chloride: Isolation of the O-trimethylsilyl salt 92

Under stirring, nitrogen and ice-cooling, trimethylsilyl

chloride (5 ml, excess) was added to a solution of 1-phenyl-1,2,3,5-tetrahydro-5-oxoimidazo-[2,1-b] quinazoline 88 (2.0g, 7.6 m mol) in dry ether (20 ml), the reaction mixture left stirred for 1 hr, filtered, washed with hexane and dried in vacuo to give 1.7g (60.13%) of the o-trimethylsilyl salt 92 as white needles, mp. 253°C.

ir : ν_{max}(KBr) cm^{-1}: 2300-2700 (br)(salt).

C. Attempted reduction of 92 with $NaBH_4/CH_3OH$: Isolation of 88

A solution of $NaBH_4$ (1.0g, 28 m mol) in dry methanol (10 ml) was added to a stirred and ice-cooled suspension of 92 (1.5g, 4 m mol) in dry ether (25 ml). The reaction mixture was treated with acetic acid (1 ml), evaporated in vacuo, admixed with water and extracted with CH_2Cl_2 (3x50 ml), dried ($MgSO_4$) and evaporated to give 0.97g (92%) of 88, mp. 164°C.

CI. Attempted reduction of the o-trimethylsilyl salt 92 with Diborane

Under nitrogen, stirring and ice-cooling, a 1.6M THF solution of diborane (5.5 ml, 12.5 m mol) was added to a solution of 92 (1.0g, 2.8 m mol) in dry THF, left stirred for 6 hr, adjusted to pH 4-5 with acetic acid, solvents evaporated in vacuo, the residue dissolved in water, extracted with CH_2Cl_2, dried ($MgSO_4$) and evaporated to give 0.9g (87%) of 88, mp. 165°C.

CII. Reaction of the trimethylsilyl salt 51 with $NaBH_4$: Isolation of 3-Allyl-1,2,3,4-tetrahydro-4-oxoquinazoline (91)

Under stirring and ice-cooling, a solution of $NaBH_4$ (2g, 52.6 m mol) in methanol (15 ml) was added to a suspension of 51 (1.3g, 4.4 m mol) in dry ether (25 ml), left stirred at rt overnight, admixed with acetic acid (2 ml), solvents evaporated *in vacuo*, the residue dissolved in ether, washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), evaporated and the oil distilled to give 1g (95%) of 91, bp. 200°C/0.2 mm.

ir : ν_{max}(neat) cm^{-1}: 3300 (NH), 1670 (amide carbonyl), 1640, 1610 (C=C).

nmr: δ ($CDCl_3$) 60 MHz: 4.1, 4.5 (m, m, 2H, 2H, N-CH_2-CH, N-CH_2-N), 5.2 (m, 2H, -CH=CH_2), 5.9 (m, 2H, -CH=CH_2), 6.5-8.3 (m, 4H, aromatic).

F. REFERENCES

1. D.A. Goldthwait, J. Biol. Chem., 222, 1051 (1956).
2. S.C. Hartman and J.M. Buchanan, J. Biol. Chem., 233, 451(1958)
3. S.C. Hartman and J.M. Buchanan, J. Biol. Chem., 233, 456(1958)
4. L. Warren and J.M. Buchanan, J. Biol. Chem., 229, 613 (1957).
5. H.M. Rauen and L. Jaenicke, Hoppe-Seyler's Z. Physiol. Chem., 293, 46 (1951).
6. B. Levenberg and J.M. Buchanan, J. Biol. Chem., 224, 1019 (1957).
7. L.N. Lukens, III and J.M. Buchanan, J. Biol. Chem., 234, 1799 (1959).
8. L.N. Luckens and J.M. Buchanan, J. Am. Chem. Soc., 79, 1511 (1957).
9. L.N. Luckens, III and J.M. Buchanan, J. Biol. Chem., 234, 1791 (1959).
10. R.W. Miller, L.N. Lukens and J.M. Buchanan, J. Am. Chem. Soc., 79, 1513 (1957).
11. R.W. Miller, L.N. Lukens and J.M. Buchanan, J. Biol. Chem., 234, 1806 (1959).
12. S.C. Hartman and J.M. Buchanan, J. Biol. Chem., 234, 1812 (1959).
13. L. Warren, J.G. Flaks and J.M. Buchanan, J. Biol. Chem., 229, 627-40 (1957).
14. J.G. Flaks, M.J. Erwin and J.M. Buchanan, J. Biol. Chem., 229, 603 (1957).
15. V. Lagerkvist, J. Biol. Chem., 233, 138 (1958).

16. B. Magasanik, H.S. Moyed and L.B. Gerhing, J. Biol. Chem., 226, 339 (1957).

17. R. Abrams and M. Bentley, Arch. Biochem. Biophy., 79, 91 (1959).

18. A. Kornberg, J. Biol. Chem., 182, 805 (1950).

19. V. Lagerkvist, J. Biol. Chem., 223, 143 (1958).

20. C.E. Carter and L.H. Cohen, J. Biol. Chem., 222, 17 (1956).

21. R.W. Miller and J.M. Buchanan, J. Biol. Chem., 237, 491(1962

22. B.N. Ames, R.G. Martin and B.J. Garry, J. Biol. Chem., 236, 2019 (1961).

23. D.W.E. Smith and B.N. Ames, J. Biol. Chem., 240(7), 3056 (1965).

24. D.W.E. Smith and B.N. Ames, J. Biol. Chem., 239(6), 1848 (1964).

25. J.E. Hodge, Advances in Carbohydrate Chemistry Vol. 10, 169 (1955).

26. H.S. Moyed and B. Magasanik, J. Biol. Chem., 235, 143 (1960)

27. H.S. Moyed and B. Magasanik, J. Am. Chem. Soc., 79, 4812 (1957).

28. B.N. Ames, J. Biol. Chem., 228, 131 (1957).

29. B.N. Ames and B.L. Horecker, J. Biol. Chem., 220, 113 (1956)

30. B.N. Ames, J. Biol. Chem., 226, 583 (1957).

31. E. Adams, J. Biol. Chem., 207, 829 (1954).

32. E. Adams, J. Biol. Chem., 217, 325 (1955).

33. Niementowski, J. Prakt. Chem., 51(2), 564 (1895).

34. W.L.F. Armarego, J. Appl. Chem., 11, 70 (1961).

35. J.S. Morley and J.C.E. Simpson, J. Chem. Soc., 360 (1948).

36. J. Maillard, R. Morrin, M. Vincent and M. Bernard, U.S. Patent, 30, 47, 462 (1962); Chem. Abstr. 58, 1474f (1962).

37. M.L. Beri, K.S. Narang and J.N. Ray, J. Ind. Chem. Soc., 12, 395 (1935).

38. F. Farooqui, unpublished results.

39. B.R. Baker, M.V. Querry, A.F. Kadhish and J.H. Williams, J. Org. Chem., 17, 35 (1952).

40. A.B. Sen and S.B. Singh, J. Ind. Chem. Soc., 42, 409 (1965).

41. D. Ranganathan, S. Ranganathan and S. Bamezai, Tetrahedron Lett. 23, 2789 (1982).

42. W.L.F. Armarego, Fused Pyrimidines, Part I, Quinazolines, Ed. D.J. Brown, p.102, Interscience Publishers (1967).

43. K. Hasspacher, Ger. 1, 102, 755 (Cl 12 p), Chem. Abstr. 56, 484 (1962).

44. S. Somasekhara, V.S. Dighe and S.L. Mukherjee, Current Science (India), 33, 209 (1964).

45. S.E. Cairncross and M.T. Bogert, Collection, Czech. Chem. Commun., 7, 548 (1935).

46. N.J. Leonard and W.V. Ruyle, J. Org. Chem., 13, 903 (1948).

47. V.S. Dighe, S. Somasekhara, G. Bagavant and S.L. Mukherjee, Current Science (India), 33, 78 (1964).

48. L. Fieser and M. Fieser, Reagents for Organic Synthesis, Vol. I, p.4.

49. G. Heller and R. Mecke, J. Prakt. Chem., 131, 82 (1931).

50. E. Shaw and D.W. Woolley, J. Biol. Chem., 181, 89 (1949).

51. J.A. Montgomery and H.J. Thomas, J. Org. Chem., 30, 3235 (1965); E.P. Lira and C.W. Huffmann, ibid., 31, 2188 (1966); K.K. Oglive, S.L. Beaucage and M.F. Gillen, Tetrahedron Lett., 1978, 1663.

52. A.G. Beaman and R.K. Robins, J. Appl. Chem., 12, 432 (1962).

53. Y. Fujimoto, Jap 6918 (1967) (Cl 16E 611.2); Chem. Abstr. 67, P82223v.

54. J.A. Montgemery and C. Temple, J. Am. Chem. Soc., 83, 630 (1961).

55. R.K. Robins, E.F. Godefroi, E.C. Taylor, L.R. Lewis and A. Jackson, J. Am. Chem. Soc., 83, 2574 (1961).

56. In view of the fact, that the 9-atom purine frame work is almost entirely divided between carbon and nitrogen, Claisen rearrangements offers possibilities for migration of the carbon residue to either proximate carbon or nitrogen. In the case of guanine the presence of the additional nitrogen at the 2-position permits migration of the carbon residue to this centre as well via a Sommelet type of rearrangement. The Claisen rearrangement of the 2,6-diallyloxy-7-methyl-purine and several analogues of this system have been reported to undergo bis [3,3] shift leading to 1,3-disubstituted-2,6-dioxo tetrahydropurines. (E. Bergmann and H. Heimbold, J. Chem. Soc., 1935, 1365).

Similar studies in the unprotected guanine system is reported to give diametrically opposite results. Thus, the rearrangement of 6-allyloxy guanine and related systems thermally rearrange to the 8-substituted guanines via two consecutive O $\rightarrow$ C migrations involving also a prototropic shift. However, when the 8-position of the guanine is blocked with a methyl group N^3-substituted products arising from two consecutive Claisen rearrangements are formed as

well as the 7-substituted guanines *via* sequence involving a [3,3] shift followed by a [3,2] shift. Interestingly, 6-benzyloxy guanine leads to the formation of N^2-benzyl-guanine arising from a [3,3] shift to nitrogen followed by a Sommelet type of rearrangement. (C.R. Fribart and N.J. Leonard, J. Am. Chem. Soc., 95, 7174 (1973); ibid, 96, 5894 (1974); B.N. Holmes and N.J. Leonard, J. Org. Chem., 41, 568 (1976).

In view of the above, the smooth [3,3] sigmatropic O → N rearrangement of 6-allyloxy-9-benzylpurine to 1-allyl-9-benzyl-6-oxopurine (40) whose structure has been established by direct synthesis is noteworthy.

57. J.A. Montgomery and C. Temple, J. Am. Chem. Soc., 79, 5238 (1957).

58. H.J. Schaefer and R.D. Weimar, J. Org. Chem., 25, 774 (1960).

59. J.A. Montgomery and H. Thomas, J. Org. Chem., 30, 3235 (1965).

60. J.A. Montgomery and H. Thomas, J. Org. Chem., 28, 2304 (1963).

61. K.L. Carraway, P.C. Huang and T.G. Scott, Synthetic Procedures in Nucleic acid Chemistry, Vol. I, p.3, Interscience Publishers (1968).

62. N.J. Leonard, K.L. Carraway and J.P. Helgeson, J. Heterocyclic Chem., 2, 291 (1965).

63. Mujake and Shimizu, Chem. and Pharm. Bull. (Japan); 18, 1446 (1970).

64. Hammer et al., J. Chem. Soc., 1932, 251; C.F. Koelsch, J. Am. Chem. Soc., 67, 1718 (1945); Sen and Upadyaya, J. Ind. Chem. Soc., 25, 437 (1948); ibid, 27, 40 (1950); Mustafa et al., J. Am. Chem. Soc., 77, 1612 (1955); J.K. Kacker and I.S. Zaher, J. Chem. Soc., 1956, 415; Abdel Majeed et al, J.Chem. Soc., C 1971(6), 1055.

65. E.S. Chipper, U.S. 3,226,394 (Cl. 260-295) Dec. 28, 1965 Chem. Abstr. 64:P8153h.

66. P. Hanumanthu, S.K.V. Seshavatharam, C.V. Ratnam and N.V. Subba Rao, Proc. Ind. Acad. Sci., 84A(2), 57 (1976); H. Bohme and H. Boing, Arch. Pharm., 293, 1011 (1960).

67. G. Heller, Wikohler, S. Gottfried, H. Arnold and H. Herrmann, J. Prakt. Chem., 120, 49 (1928), Chem. Abstr. 23, 835 (1928); G. Heller and R. Mecke, ibid, 126, 76 (1930), Chem. Abstr., 24, 2747 (1940); ibid, 131, 82 (1931).

68. D.T. Zentmyer and E.C. Wagner, J. Org. Chem., 14, 967 (1949).

69. O. Yu. Magidson and E.S. Golovchinskaya, J. Gen. Chem., (U.S.S.R.) 8, 1797 (1938).

70. M.T. Bogert and G. Satchard, J. Am. Chem. Soc., 41, 2052 (1919).

71. E.B. Womack, N. Campbell and G.B. Dodds, J. Chem. Soc., 1402 (1938).

72. H. Herbert Fox and J.T. Gibas, J. Org. Chem., 17, 1653(1952).

73. T. Higashino, Chem. Pharm. Bull (Japan), 9, 635 (1961).

74. S. Asano and H. Asai, Japan. Pat, 3376 (59); Chem. Abstr., 54, 14277 (1960).

75. B.Kh. Zharekeev, M.V. Telezhenetskaya and S.Yu. Yunusov, Khim. Phir. Soedin. 1973, 279; Chem. Abstr. 79, 321582e; D.R. Mehtha, J.S. Naravane and R.M. Desai, J. Org. Chem., 28, 445 (1963); R.R. Arndt, S.H. Eggers and A. Jordaan, Tetrahedron, 23, 3521 (1967); B. Loev, T. Jen and R.A. Mclean, Experienha, 27, 875 (1971); T. Onaka, Tetrahedron Lett., 4387 (1971).

76. Griess, J. Prakt. Chem., 5(2), 369 (1972).

77. N.A. Lange and F.E. Sheibly, Org. Syn., Coll. Vol. II,p.79.

78. K. Butler and M.W. Partridge, J. Chem. Soc., 1516 (1959).

79. R.J. Grout and M.W. Partridge, J. Chem. Soc., 3548 (1960).

80. ibid; p.3551 (1960).

81. B. Loev, T. Jen and R.A. McLean, Experientia, 27(8), 875 (1971).

VITAE

I, Krishnan Kesavan, was born on 5th May 1950 in Madras. I obtained my B.Sc. Degree from Loyola College, Madras University (1970) and M.Sc. Degree from Presidency College, Madras University (1972). I joined the Tamil Nadu Government Service as Assistant Professor of Chemistry in 1975. I joined the Department of Chemistry, I.I.T. Kanpur as a Research Scholar, under the Faculty Improvement Programme of the University Grants Commission in January 1979. I am at present working in Govt. College, Vriddhachalam, Tamil Nadu as Assistant Professor of Chemistry.